Substance Abuse and Chronic Pain

Until the 1980s, medical (and particularly state board of medical examiners) dogma was that the long-term use of opioids for chronic benign pain was always inappropriate. Practitioners who prescribed long-term opioid therapy, other than for cancer patients, were frequently investigated and sanctioned.

Beginning in the late 1980s, it became apparent that many patients with chronic pain improved markedly when given sufficient opioids for pain control and that they continued to benefit for years without significant problems. Many clinicians were surprised to find that the dosage requirements of these patients did not continually increase but rather remained stable. Clinicians who had been incorrectly trained to believe that taking opioids for a prolonged period would always result in addiction were surprised that most of these patients never exhibited any signs or symptoms of addictive disease.

The use of opioids to control chronic benign pain became even more common in the 1990s, as long-acting opioid preparations became readily available. The Joint Commission on Accreditation of Healthcare Organizations has issued guidelines on how to assess and manage pain. These guidelines require assessing the nature and intensity of the pain, establishing and using pain management procedures, and monitoring patient response to the pain intervention. A "Bill of Rights" asserting that patients had a right to effective pain control was adopted in many states. In most other states, the medical examiner boards eased prescribing guidelines. Some clinicians were even sued successfully for failing to prescribe sufficient opioid medications to control a patient's pain.

At the end of the 1990s, however, the increasing frequency of diversion and abuse of opioid medications, particularly OxyContin®, drew widespread public attention. Successful criminal prosecution of clinicians for indiscriminately prescribing opioids occurred, and federal and state drug enforcement agencies actively investigated many clinicians who prescribed large quantities of opioids. As a result, many clinicians became afraid to prescribe opioids for chronic benign pain.

Most clinicians have only a superficial understanding of what substance abuse really is, are not skilled at recognizing the symptoms of the problem, and have no knowledge of the diversion and illicit resale of controlled medications. Most

clinicians do not know the laws and statues regarding prescribing controlled substances, because the subject is rarely covered in medical school or in continuing medical education courses. Similarly, many are unaware of their legal responsibilities when they become aware that patients in their practice have a substance abuse problem.

The responsibility for knowing state and federal regulations regarding prescribing, dispensing, or administering controlled substances ultimately lies with the clinician. However, the Federation of State Medical Boards specifically states that clinicians should not fear disciplinary action for ordering, prescribing, or administering controlled substances for a legitimate medical purpose in the course of professional practice. Prescribing and administering controlled substances for pain are legitimate if prescribed for a medical purpose. Prescribing should be done in the context of a diagnosis and documentation of unrelieved pain as part of a physician-patient relationship. (Federation of State Medical Boards 2004)

Demographics of Substance Abuse

The epidemic of drug abuse that exists today is a relatively modern phenomenon, first beginning in the mid 1800s and accelerating rapidly during the 1960s. Despite perennial declarations of a "war on drugs," since that time, the epidemic of drug abuse has continued. During the past 20 years, data have consistently shown that about 7.5% (7.9% in 2005) of the U.S. adult population has a significant substance abuse problem. The national Institute on Drug Abuse (NIDA) found that between 1990 and 1996 there was no change in the number of Americans (about 15 million) who were considered substance abusers. However, in the most recent NIDA report in 2005, a reported 19.7 million Americans reported current or recent (past month) illicit drug use.

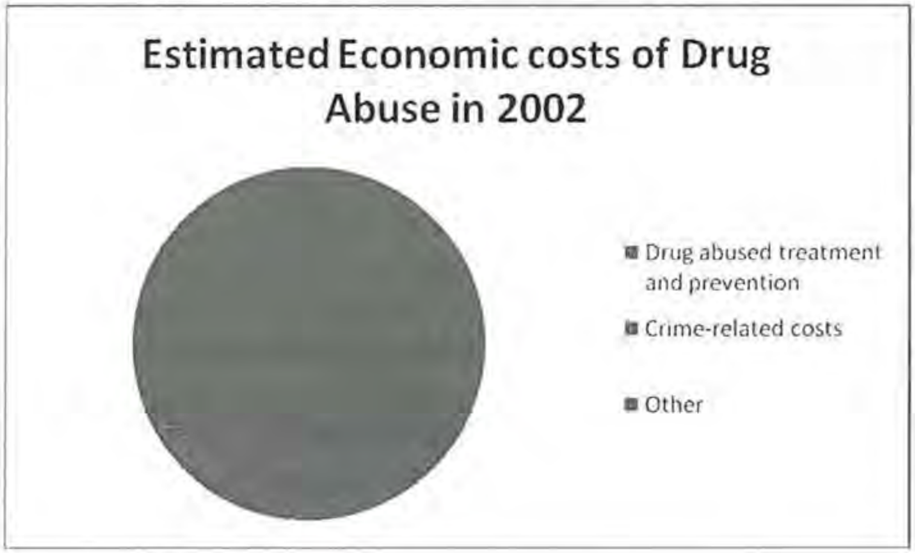
Marijuana has remained the most commonly used illicit drug since the 1960s, with about 2.4 million Americans beginning marijuana use each year. However, the use of other illicit drugs shows distinct historical trends. During the 1960s, abuse of hallucinogens, such as lysergic acid diethylamide (LSD) and peyote was common. In the 1970s, opioids and amphetamines were the most frequently abused drugs. During the 1980s, powder cocaine became the most commonly abused drug, reaching a peak of 5.7 million American users in 1985, then slowly falling in popularity. During the late 1980s and early 1990s, "crack" cocaine use reached epidemic proportions with

more than 600,000 users in 1997. In 2005, an estimated 900,000 individuals reported using cocaine. Recently, methamphetamine use has grown in popularity, with approximately 512,000 persons reporting use in 2005.

In recent years, the frequency of opioid abuse has increased dramatically. Heroin use in the United States increased from 68,000 persons in 1992 to 216,000 in 1996. According to the National Survey on Drug Use and Health (NSDUH), the number of current heroin users was steady at about 136,000 during 2004 and 2005. The number of current heroin users increased to 338,000 in 2006. Estimated lifetime use of heroin was 2,506,000 in 2005 and 3,947,000 in 2006. (Substance Abuse and Mental Health Services Administration;SAMHSA 2006)

Diverted prescription opioids, while always a problem, have become the predominant source of opioids in many areas of the country. The NSDUH estimates that the incidence of lifetime OxyContin® abuse was 3.1 million in 2004. In the month before the 2004 NSDUH survey of nonmedical use of prescription drugs, 4.4 million individuals used pain relievers, 1.6 million used tranquilizers, 1.2 million used stimulants, and 0.3 million reported using sedatives. The severity of the problem of prescription drug abuse has made opioid diversion the focus of both the lay press and law enforcement agencies in recent years.

The financial cost of substance abuse to society remains high. The U.S. government estimates that the economic cost of drug abuse in 2002 was $180.9 billion, representing the use of resources for health and crime consequences as well as loss of productivity, disability, and death. Approximately $9 billion dollars are spent each year on drug abuse treatment and prevention. In 2002, the U.S. government estimated that crime-related costs of drug abuse were estimated to be $107 billion.



Definitions of Substance Abuse and Dependence

Scientific efforts to understand substance abuse began only during the epidemic of drug abuse that began in the 1960s. Concepts and terminology in the field are constantly changing to reflect the improved understanding of substance abuse. The term *narcotic* is rarely used by addictionologists (although it remains in use by law enforcement agencies and court systems). Medically, *narcotic* refers to a drug of the opioid class; legally, the term refers to any illicit drug.

Although the term *addiction* or the *disease of addiction* remains in widespread use among clinicians and the lay public it is no longer used by the American Psychiatric Association or by addictionologists. Currently, the terms *substance abuse* and *substance dependence* are used for medical diagnosis.

Substance abuse is defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders as a maladaptive pattern of chemical substance use that significantly interferes with a person's life as indicated by at least one of the following:

- Neglect of work, school, or home obligations
- Use of the substance in a hazardous situation (e.g., driving, operating machinery)
- Repeated substance-related legal problems

- Continued use of the substance despite harmful, recurrent social or interpersonal problems associated with its use.

Although no single cause of substance abuse exists, substance abuse has definite associations with certain psychological and social factors. Abusers are more likely than nonusers to have a history of depressive illness or bipolar disorder. They are also more likely than others to have a family history of psychiatric illness or substance abuse or to have suffered traumatic or disruptive events during childhood. Abuse or neglect as a child is a strong predictor of substance abuse as a young adult. (Lo 2007, Hussey 2006)

Substance dependence is defined as opioid use that is associated with tolerance to the substance's effect or withdrawal symptoms if the substance is discontinued. Care should be taken to differentiate physical withdrawal symptoms from substance craving. Craving is an extremely strong psychological desire to use the substance, but is not a physical symptom.

Craving is an extremely strong psychological desire to use the substance, but is not

Withdrawal symptoms vary according to the substance in question. Although all patients are different, opioid withdrawal symptoms typically begin to appear within 8 to 16 hours of the last dose of opioid; many abusers, for example, wake up each morning in mild withdrawal. Peak withdrawal effects, which occur within 36 to 72 hours, include nausea, vomiting, diarrhea, watery eyes, runny nose, and coughing. Muscle aches and twitching, including abdominal cramps and jerking of the legs, are common. Chills, profuse sweating, and "goose bumps" occur in most cases. (The chills and goose bumps lead to the phrase "cold turkey" that is sometimes used to describe going through opioid withdrawal.) Irritability and mild elevations of body temperature, blood pressure, and respiratory rate also occur.

Physical withdrawal generally, but not always, resolves within 5 to 8 days and is not considered life-threatening. Nonetheless, these withdrawal symptoms are uncomfortable and unpleasant, and management of the symptoms is desirable. Medically, treatment of withdrawal symptoms is a straightforward process that can usually be accomplished with minimal difficulty. Detoxification is usually performed by reducing the opioid dosage by 10% to 20% each day, with the entire process requiring 5 to 10 days for completion. Almost any opioid can be used for detoxification because they all have some degree of cross-tolerance. The alpha-2 agonist clonidine (Catapres®) has been shown to reduce the severity

of withdrawal symptoms and is often used in conjunction with the above medications.

An alternative method for treatment of withdrawal, which is available only in certain centers, involves heavily sedating the patient (to a near anesthetic level) and administering naloxone or naltrexone to precipitate withdrawal while the patient is unconscious. Although this method is quite expensive and is not covered by insurance plans, it shortens the course of withdrawal to less than 48 hours. Antagonist-induced withdrawal done under sedation also has an increased risk of serious or even life-threatening adverse events without clear benefit. (Gowing 2006)

Although the physical withdrawal symptoms are largely resolved within a week, it is extremely important to realize that simply overcoming withdrawal does not stop drug dependence. Approximately 95% of substance abusers who "detoxify" (overcome withdrawal symptoms) will relapse within 3 months unless they receive other treatment. Because they do not suffer from severe psychological drug cravings, most chronic pain patients can be tapered from their opioid medications at home, even though they may experience some withdrawal symptoms. Substance abusers, on the other hand, can rarely detoxify except in a controlled environment where it is absolutely impossible for them to obtain their drug of choice. Lifestyle changes must accompany the withdrawal process to help the individual maintain sobriety/abstinence.

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Complications of Substance Abuse

The most common complications of substance abuse are accidents caused by intoxication. Studies have shown that as many as 50% of all hospital trauma admissions have positive urine drug screens. Impaired motor coordination, decreased inhibition, and altered reasoning ability occur with most forms of intoxication but are most pronounced with sedatives and alcohol. (McGeary 2000) Opioid intoxication also interferes with normal bodily functions such as breathing and swallowing. With chronic use, nearly all side effects diminish or stop, with the notable exceptions of miosis and constipation.

Suicide is also a frequent cause of death among substance abusers but accidental overdose is probably a more common cause of death. Opioid overdose causes

pinpoint pupils, slowed respirations (often only 2 to 4 breaths per minute), slowed heart rate, and sedation. If untreated, the overdose will progress to coma and respiratory arrest, followed by cardiac arrest and death.

Diagnosis of Substance Abuse

Substance abuse is a surprisingly common condition. The lifetime prevalence of substance abuse (which includes alcoholism and drug abuse) among the adult population is almost 15%. At any given time, about 7.5% of adults have a substance abuse problem. In 2005, the NSDUH survey found that approximately 8.1% of the population of the United States had abused an illicit drug during the month before the survey interview. More than one-half of all substance abusers use prescription drugs, sometimes in addition to alcohol or illicit substances. Given the high fatality rates among substance abusers, getting them to proper treatment can be a life-saving measure.

More than one-half of all substance abusers use prescription drugs, sometimes in addition to

Unfortunately, many clinicians fail to investigate the possibility of substance abuse thoroughly and do not make appropriate referrals when they do discover it. When the diagnosis of substance abuse is not considered, these patients are often thought to have primary psychological problems or are simply considered "difficult patients."

Too often, even when the diagnosis becomes obvious, the clinician's response is simply to "fire" the patient rather than to suggest substance abuse treatment. This may be because most clinicians are not fully aware of the success rates of substance abuse treatment and the potential savings, both in dollars and lives, which it offers. Nevertheless, the standards established by the American Medical Association and the American Society of Addiction Medicine state that referral to a treatment program is the minimal acceptable standard of care once substance abuse is diagnosed. Simply discharging a patient with an abuse problem from the practice can place the clinician at risk of "failure to diagnose" and "failure to treat" lawsuits.

Detecting Substance Abuse in a Chronic Pain Practice

Although patients rarely admit that they have substance abuse problems, there are some consistent signs associated with substance abuse that the clinician should watch for. These include changes in mental status, recent accidents or trauma, a history of

poor impulse control (legal difficulties, gambling, losing jobs), and a history of poor or unpredictable response to standard pain therapies. Patients with a past history or strong family history of substance abuse (including alcohol abuse) are far more likely to have a substance abuse problem than
others are.

Similarly, patients with substance abuse problems are likely to have a history of "allergy" or adverse side effects to many different opioids, leaving only 1 or 2 that they say they can take. Substance abusers tend to claim that extended-release medications, such as KADIAN®, are ineffective, whereas immediate-release medications such as hydromorphone or OxyContin® (which becomes immediate-release if broken or swallowed) are effective.

In a few cases, it is obvious the patient has a problem. Patients who have altered a prescription or have obtained opioid prescriptions from multiple clinicians, no matter how valid their reasons for doing so, have committed a felony. A clinician in such circumstances should not continue to prescribe for the patient, and may have a legal obligation to report the patient's actions to law enforcement authorities. Informing the patient of the criminal possibilities involved may break through any denial and get the patient to acknowledge the problem.

Factors Associated with Opioid Abuse

The cause of opioid abuse has been debated for many years. Although there is no single cause, certain predisposing factors are well documented. Family dysfunction during childhood and a family history of drug or alcohol abuse are common among opioid abusers. Up to 90% of opioid abusers have some form of psychiatric illnesses, including major depressive disorder, anxiety disorder, and personality disorder. A family history of depression or psychiatric illness is also common. Recent research also indicates that there may be a genetic predisposition to opioid abuse, because abusers have different central nervous system responses to opioids than do nonabusers. (Kreek 2007)

Practical Issues with Chronic Opioid Use

Chronic opioid therapy for properly selected chronic pain patients appears to be an obvious and medically appropriate treatment option because such therapy offers pain

control and improved quality of life. However, there is disagreement about how appropriate this therapy is. Some clinicians feel the vast majority of chronic benign pain patients should receive long-term opioid therapy. Others feel it is rarely indicated because the risks outweigh the benefits.

Most clinicians agree that the incidence of opioid abuse is low. A few poorly designed studies in the early 1990s even suggested that chronic pain patients "almost never" developed opioid abuse problems. In reality, these studies usually reflected the experience of a single, rather exclusive pain center, or used very superficial definitions of abuse, such as "percent of patients arrested." Many other studies show significantly higher rates of abuse. Some have claimed that as many as 20% of patients requesting chronic opioid therapy have a substance abuse problem. The true incidence of abuse probably varies widely in different practices, depending on factors such as the geographic location, the type of patients seen, and the vigilance of the practitioners involved.

The clinician is left, therefore, to make decisions based on his or her best medical judgment in each individual case. Most pain practitioners agree that when dealing with benign pain the problem is simplified if the decision to initiate and then continue chronic opioid therapy is based on improvements in the patient's ability to function rather than change in subjective pain level. A patient who has wild mood swings when taking medications or who has frequent falls or accidents cannot be considered to have improved quality of life on chronic opioid maintenance.

On the other hand, most chronic benign pain patients do have markedly improved ability to function when maintained on chronic opioid therapy. Being able to perform simple tasks like cleaning the house or being able to shop can make a huge difference in lifestyle and the patient's sense of self worth. Determining if the patient's ability to function is improved should involve questioning not only the patient but also close family members.

Differentiating Use from Abuse

Rarely does any single sign clearly identify a patient with substance abuse problems during the initial evaluation. Rather, a pattern consistent with substance abuse may become evident as the clinician works with the patient over time (Table 6-2). Those patients with past histories or strong family histories of substance abuse and psychiatric illness are more likely to suffer from the disease of addiction. Similarly, a

social history of personal and familial dysfunction or personality disorder is associated with a high incidence of substance abuse.

It must always be remembered, however, that most substance abusers manage to hide their problem for months or years before it becomes evident to outsiders. For this reason, it is strongly recommended that input from the patient's spouse or close relatives be obtained whenever possible. Many practices require not only the patient but also the patient's spouse sign the controlled substances agreement. This not only involves the spouse with the clinician, it provides some protection should a claim later be made by the same spouse that the doctor "should have known" the patient had a substance abuse problem.

Note that persons who are not themselves opioid abusers but who obtain prescriptions for illicit resale are keenly aware of which clinicians in any area are willing to prescribe medications with a high street value. Often, these persons appear to be model patients, answering every question in a manner that will ensure their continued supply. Random urine drug screens are the most effective tool for detecting such individuals, because an appropriately chosen screening panel will be negative for the opioid that is being prescribed.

Table 6-1

Signs Associated with Substance Abuse
Repeated requests for short-acting medications (Hydrocodone is considered short-acting when abused by chewing or breaking the tablet).
Repeated incidences of early refill requests, especially when the patient has "typical" excuses such as "the pills fell in the toilet," "the dog ate them," or "someone stole my medicine."*
Frequent telephone calls, particularly after hours or on weekends.
Frequent requests to change medication because of side effects or lack of efficacy.
More than a single incidence of other clinicians prescribing opioids.
Patient's past history of substance or alcohol abuse.
History of preexisting psychiatric illness, especially bipolar disorder, schizophrenia, or personality disorder.
Family history of substance or alcohol abuse or strong family history of psychiatric illness.
Social history of dysfunctional or high-risk behaviors, including multiple arrests, multiple marriages, abusive relationships (either abuser or victim), inability to maintain employment, and multiple accidents.

* *Such excuses require a police report to substantiate the facts. Even with a police report, most practitioners are unwilling to refill more than one "incident" per year.*

Table 6-2

Signs and Symptoms Consistent with Pseudoaddiction
Complaints that pain medication is ineffective.
Hoarding or repetitively counting medications.
One or possibly 2 incidences of running out of medications early, especially if the patient states honestly that he or she took more than prescribed.
Obsessing about the duration of time until medication refill.
A single incidence of obtaining opioids from another source, not repeated after the patient is warned of the consequences.

The classic signs and symptoms of drug abuse may be difficult to differentiate from the symptoms of chronic pain, especially when depression or other psychological illness is present. Pseudoaddiction is a set of behaviors that are often exhibited by patients with inadequately treated pain, including patients with cancer pain. Pseudoaddictive behaviors (Table 6-2) should not be considered signs of abuse in a chronic pain patient, but rather should be considered symptoms of inadequate treatment unless they are accompanied by other signs of abuse.

> Pseudoaddiction is a set of behaviors that are often exhibited by patients with inadequately treated pain, including patients with

Documentation and Monitoring

Although what constitutes appropriate prescribing of opioids remains a frequently debated topic, the guidelines requiring proper medical documentation of controlled substances are quite clear. As with every other aspect of medicine, if the medical record does not contain the proper documentation, it will be assumed by regulating authorities that the clinician did not obtain or act on the information in question. In fact, clinicians are more likely to be sanctioned by state medical boards for poor documentation than for overprescribing.

The Federation of State Medical Boards produced guidelines for the use of controlled substances in 1998, which have become a standard for the use of chronic opioids. A similar document was endorsed by the American Academy of Pain Medicine and the American Pain Society in 1999 (see Appendix 6-1). The American Pain Society has since published additional updates for management of arthritis pain (2002), for fibromyalgia syndrome (2005), and for cancer pain patients (2005). In general, the following guidelines, which are similar to those presented in earlier chapters, are consistent with both of these group's guideline requirements for documentation.

Evaluation

The patient evaluation should include a description of the pain, including its effect on the patient's ability to function; any current or past treatments and their effects; the indication for opioid therapy; and whether the patient has a past or family history of substance abuse. The Federation of State Medical Boards suggests the following steps in the evaluation of a patient with chronic pain. 1) Evaluation of the patient. This should include a physical examination and a medical history. The medical record should contain documentation about the nature and intensity of the pain, current and

past treatments, and any history of substance abuse or risk factors for abuse. 2) Treatment plan. This should include the goals of management. 3) Informed consent and agreement for treatment. The physician should discuss the risks and benefits of opioid treatment and outline the patient responsibilities including follow up and prescription management (e.g. refills). 4) Periodic review. The physician should periodically review the progress toward treatment objectives and modify the plan accordingly. 5) Consultation. Patients should be referred as necessary to achieve treatment objectives. 6) Medical records. The physician should keep accurate, current, and complete medical records regarding all aspects of patient management. (FSMB 2004)

Treatment Plan

The treatment plan should include not only the agents to be used, but also the expected effects and side effects. The treatment plan must include how frequently the clinician will modify agents or dosing regimens and what the goals of therapy are, including what would be considered sufficient improvement to continue therapy (improvement should be defined as change in function, not simply "pain relief").

Informed Consent

An informed consent should be obtained before initiating chronic opioid therapy. At a minimum, the consent must make the patient aware of the possibility of the potential for physical dependence and the possibility of withdrawal symptoms. It should also include a warning that opioid therapy could trigger relapse among ex-abusers or substance abuse among those with a strong family history of the disease.

Opioid Agreement

An opioid or controlled substance agreement should be part of the medical record (an example is included in Appendix 6-2). The agreement should include the informed consent, the rules regarding medication use, and the reasons for which the clinician will terminate care. It should also include permission for the clinician to contact any pharmacy to confirm the patient's medications and a statement that the patient will undergo drug screens whenever requested.

Medication List

A written list of every controlled substance prescription must be kept in the patient's chart. Many centers recommend that duplicate prescriptions be used for controlled substances and a copy placed in the chart. Alternatively, computerized prescription writing systems are readily available that keep the patient's medication record immediately accessible. Many states only allow duplicates to be issued through the state.

Chart Review

Periodic review of the chart should contain regular reviews of the patient's benefits (or lack of benefits) from opioid therapy. If the treatment goals established are not met, the clinician must document why he or she believes continued opioid therapy is indicated. The patient (and spouse, if possible) should be seen in the office regularly. Although there is no clear guideline for exactly how often the patient receiving chronic opioid therapy should be seen, many centers require an appointment every 30 days, whereas some allow more established patients to be seen every 90 days.

Investigation of Questionable Behavior

Consultation should be obtained if the clinician suspects the patient may have a substance abuse problem. Other actions taken to investigate any incidence of questionable behavior (lost or stolen medications, frequent requests to change medication) should be documented in the chart. These may include "sweeps" of area pharmacies to ensure that the patient is not obtaining other medications, counseling sessions with the patient and spouse, and drug screens.

Choice of Opioid

Despite the claims of some manufacturers, any member of the opioid group can be abused. Some tablets, such as Immediate-release morphine (MSIR®), hydromorphone (Dilaudid®), oxycodone (OxyContin®), and Meperidine (Demerol®), can be dissolved and injected by abusers. There are far more oral than parenteral abusers. Many of these persons are not part of the illicit drug trade, but instead obtain opioids from multiple clinicians, often under false pretenses. Hydrocodone (Vicodin®, Lortab®, Tussionex®), meperidine, oxycodone (OxyContin®, Percocet®), and hydromorphone are all commonly abused.

Every opioid has the potential to

Every opioid has the potential to be abused, including those considered "agonist-antagonists," such as butorphanol, and those considered "mild," such as codeine or propoxyphene. Nevertheless, there are clearly "drugs of choice" that are preferred by persons who abuse opioids. Similarly, certain opioids have extremely high illicit values when sold on the street, whereas others have little or no value. Street values and choices of abused drugs do tend to vary somewhat at different times and in different locations, but certain trends are constant.

As a rule, short-acting opioids are strongly preferred by abusers to time-release or extended-duration medications. Historically, hydrocodone is the most widely abused opioid, probably because as a schedule III medication used for both pain control and cough suppression, it is more available than other agents. Hydromorphone has been the preferred prescription opioid abused by injection for over a decade. Intravenous drug abusers strongly prefer nongeneric Dilaudid™ because it dissolves in water more readily than generic versions.

Since 1999 OxyContin® has arguably become the most commonly abused and diverted opioid, particularly in noncoastal states. Although OxyContin® is marketed as a controlled-release formula, the medication becomes immediate-release if the pill is crushed or chewed. OxyContin® abuse, which tends to be common in young adults, has been associated with a high number of accidental deaths.

Truly long-acting agents, such as KADIAN® or Duragesic®, are not preferred by abusers because they do not get a "rush" from the slow onset of these medications. However, enterprising abusers with some knowledge of "street lab" chemistry can remove the active agent.

Although there certainly are some legitimate patients who are unable to take any of the long-acting opioids, the vast majority of chronic pain patients obtain effective relief with these agents.

Opioids in Patients with a History of Substance Abuse

The two major issues concerning chronic opioid therapy in persons with a history of substance abuse come from opposite ends of the spectrum. Some clinicians mistakenly believe that a history of nonopioid substance abuse, such as alcoholism, does not place the person at risk when prescribing opioids. Others believe that

persons with a substance abuse history can never take opioid agents safely. Both points of view are incorrect.

Polysubstance abuse (or "crossover addiction") occurs commonly. From 40% to 70% of substance abusers use chemicals from more than one classification. It is not clear how often exposure to a second substance will "trigger" a relapse in a person recovering from chemical dependence, but it is clear that this can and does happen. Therefore, it must be assumed that a person recovering from alcoholism is at increased risk of developing a substance abuse problem if given opioids, although it is not clear how great this risk is. (Staines 2001)

Conversely, persons in recovery from opioid abuse can successfully undergo long-term opioid therapy for chronic pain without apparent relapse. Obviously, they are at increased risk of relapse, and most pain specialists require an informed consent to be signed before beginning opioid treatment. The rate of risk is unknown and probably varies according to several circumstances: the length of recovery, the severity of the painful condition, the person's mental health state, and the presence of an adequate recovery support group.

Most addictionologists agree that long-acting or time-release agents should be used if possible when treating a recovering person. Similarly, dosing should be around-the-clock and PRN medications should be avoided. The goal is to avoid rapid changes in mood associated with "getting high" and to instead maintain a steady state dose of opioid medication.

Summary

- During the past 20 years, data have consistently shown that about 7.5% of the U.S. adult population has a significant substance abuse problem. The most recent report of the national Institute on Drug Abuse found that there was an increase in the number of Americans (about 20.4 million) who were considered substance abusers. (SAMHSA 2006)
- The Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders defines substance abuse as a maladaptive pattern of chemical substance use that significantly interferes with a person's life.
- Substance dependence is defined as opioid use that is associated with tolerance to the substance's effect or withdrawal symptoms if the substance is discontinued. Care should be taken to differentiate physical withdrawal symptoms from substance craving. Craving is an extremely strong psychological desire to use the substance, but not a physical symptom.

- Consistent signs associated with substance abuse include changes in mental status, recent accidents or trauma, a history of poor impulse control (legal difficulties, gambling, losing jobs), and a history of poor or unpredictable responses to standard pain therapies. Patients with a past history or strong family history of substance abuse (including alcohol abuse) are far more likely to have a substance abuse problem than others are.
- Clinicians should document the patient evaluation, treatment plan, informed consent, opioid agreement, and medication list. A periodic chart review should state the benefits of the opioid therapy for the patient.

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Self-Assessment Test

Circle the best response

1). What percentage of primary care clinicians state they have received no training or education concerning substance abuse?
a. 10% c. 50%
b. 25% d. 75%

2). In the late 1990s, widespread diversion of ________________ led to the prosecution of many clinicians for overprescribing.
a. Lortab®
b. Dilaudid®
c. morphine
d. OxyContin®

3). As documented over the past 20 years, what percentage of all U.S. adults has a substance abuse problem?
a. 1% c. 15%
b. 7.5% d. 25%

4). Withdrawal from opioid medications begins about _____to _____hours after the last dose of medication.
a. 4 to 6
b. 6 to 12
c. 8 to 16
d. 24 to 36

5). Peak effects of opioid withdrawal occur between _____ to_____ after the last dose of medication.
a. 24 to 36 hours
b. 36 to 72 hours
c. 4 to 6 days
d. 7 to 10 days

6). Assuming a substance abuser gets past the withdrawal phase but receives no other treatment, what are the odds that he or she will relapse within 3 months?
a. 25% or less
b. 25% - 50%
c. 50% – 75%
d. more than 90%

7). Obsessive behavior about pain medication resulting from an inadequate dose of opioid is called
a. Substance abuse
b. Addiction
c. Pseudoaddiction
d. Dependence

8). According to the State Board of Medical Examiners Guidelines, which of the following is not required documentation when a patient receives chronic opioid therapy?
a. A written evaluation
b. A psychological assessment
c. A written list of every controlled substances prescription
d. A controlled substances contract

<u>True or False</u>

9). It is a good idea to tell clinicians that KADIAN® has "low abuse potential."
a. True
b. False

10). A 22-year-old woman admitted to the hospital because of opioid withdrawal has a substance abuse problem.
a. True
b. False

11). If not treated, opioid withdrawal is likely to cause seizures, heart attack, or stroke.
a. True
b. False

12). As a general rule, abusers and diverters will prefer short-acting opioids rather than time-released opioids.
a. True
b. False

Answers to Self-Assessment Test

1. c 2. d 3. b 4. c 5. b 6. d	7. c 8. b 9. b (Never use the phrase "low abuse potential.") 10. b (Withdrawal does not automatically imply abuse.) 11. b 12. a

Appendix 6-1

Public Policy Statement on the Rights and Responsibilities of Healthcare Professionals in the use of Opioids for the Treatment of Pain.

A consensus document from the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine.

Published by the American Pain Society, 2004. Available online at: http://www.ampainsoc.org/advocacy/rights.htm. Accessed 9-25-07.

Background

Healthcare professional (HCP) concerns regarding the potential for harm to patients, as well as possible legal, regulatory, licensing or other third party sanctions related to the prescription of opioids, contribute significantly to the mistreatment of pain. HCPs are obligated to act in the best interest of their patients. This action may include the addition of opioid medication to the treatment plan of patients whose symptoms include pain. Though many types of pain are best addressed by non-opioid interventions, opioids are often indicated as a component of effective pain treatment. It is sometimes a difficult medical judgment as to whether opioid therapy is indicated in patients complaining of pain because objective signs are not always present.

A decision whether to prescribe opioids may be particularly difficult in patients with concurrent addictive disorders, or with risk factors for addiction, such as a personal or family history of addictive disorder. For such persons, exposure to potentially rewarding substances may reinforce drug taking behavior and therefore present special risks. It is, nonetheless, a medical judgment that must be made by a HCP in the context of the provider-patient relationship based on knowledge of the patient, awareness of the patient's medical and psychiatric conditions and on observation of the patient's response to treatment. The selection of a particular opioid, or combination of opioids, and the determination of opioid dose and therapeutic schedule similarly must be based on full clinical understanding of a particular situation and cannot be judged appropriate or inappropriate independent of such knowledge. All schedule II-V opioids, including methadone, may be appropriate choices for pain control in different circumstances. It is critical that clinicians

understand the special pharmacologic characteristics of each medication in order to prescribe them safely and effectively for pain.

Despite appropriate medical practice, healthcare providers who prescribe opioids for pain may occasionally be misled by patients who wish to obtain medications for purposes other than pain treatment, such as diversion for profit, recreational use or perpetuation of an addicted state. Physicians who are willing to provide compassionate, ongoing medical care to challenging and psychosocially stressed patients, where that treatment includes the prescription of opioids, assume an additional obligation to understand the risks and management of addictive disease because they risk complications of care more often than physicians unwilling to treat this population.

Addiction to opioids may occur despite appropriate opioid therapy for pain in some susceptible individuals. Persistent failure to recognize and provide appropriate medical treatment for the disease of addiction is poor medical practice and may become grounds for practice concern. Similarly, persistent failure to use opioids effectively when they are indicated as part of the treatment of pain, including in persons with active or recovering addiction, is poor medical practice and may also become grounds for practice concern. It is important to distinguish, however, between HCPs who are knowingly complicit in diversion or other illegal prescribing activities and physicians who may inappropriately prescribe opioids due to misunderstandings regarding addiction or pain. HCPs traditionally have received little or no education on addiction or clinical pain treatment in the course of training. This omission is likely a basis for inadequate detection and management of addiction and inadequate assessment and treatment of pain.

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Recommendations

1) Healthcare professionals (HCPs) who prescribe opioids for the treatment of pain should use clear and reasonable medical judgment to establish that a pain state exists and to determine whether opioids are an indicated component of treatment. Opioids should be prescribed in a lawful and clinically sound manner. Patients

should be followed at reasonable intervals for ongoing medical management, to confirm as nearly as is reasonable that the medications are used as prescribed, that the goals of treatment are met and to revise therapy as indicated. Such initial decision making and ongoing management should be appropriately documented.

2) HCPs who are practicing medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids for the treatment of pain should not be held responsible for the willful and deceptive behavior of patients who successfully obtain opioids for non-medical purposes. It is an appropriate role of the DEA, pharmacy boards and other regulatory agencies to inform physicians of the behavior of such patients when it is detected.

3) Interventions to correct the clinical care practices of HCPs who consistently fail to recognize addictive disorders, medication misuse, or medication diversion in their patients are appropriate. Interventions may include education and/or licensing or legal sanction as indicated after careful and appropriate review of records and other available information.

4) Interventions to correct the clinical care practices of HCPs who consistently fail to appropriately evaluate and treat pain in their patients are appropriate. Interventions may include education and/or licensing or legal sanction as indicated after careful and appropriate review of records and other available information.

5) For the purpose of performing regulatory, legal, quality assurance and other clinical case reviews, it should be recognized that judgment regarding a) the medical appropriateness of the prescription of opioids for pain in a specific context, b) the selection of a particular opioid drug or drugs, and c) the determination of indicated opioid dosage and interval of medication administration, can only be made properly with full and detailed understanding of a particular clinical case.

6) Regulatory, legal, quality assurance and other reviews of clinical cases involving the use of opioids for the treatment of pain should be performed, when they are indicated, by reviewers with a requisite level of understanding of pain medicine and addiction medicine.

7) Appropriate education in addiction medicine and pain medicine should be provided as part of the core curriculum at all medical and other provider training schools.

8) Legal and/or licensing actions against HCPs who are proven to be knowingly complicit in the diversion of scheduled drugs or other illegal prescribing activities are appropriate.

This document was prepared by the following committee members: Seddon Savage, MD (Chair) - APS; Edward C. Covington, MD - AAPM; Aaron M. Gilson, PhD – APS; Douglas Gourlay – ASAM; Howard A. Heit, MD - ASAM; and John B. Hunt, MD – AAPM.

Adopted by AAPM Board of Directors, March 2004
Adopted by APS Board of Directors, March 2004
Adopted by ASAM Public Policy Committee, January 2004

Appendix 6-2

A sample controlled substances agreement

The long-term use of opioids (narcotics) and benzodiazepines (tranquilizers and sleeping pills) is controversial because of uncertainty regarding their risks and benefits. Because these drugs have a risk of misuse and/or diversion, strict accountability is required on the part of the patient and clinician. The purpose of this agreement is to protect our patients' access to controlled substances, protect our ability to continue to prescribe them, and prevent the misuse and diversion of substances. There can be no exceptions to these policies, no matter how good the reasons are for wanting an exception made.

1. From this point forward, you will report receiving any controlled substances from another clinician to our office by the next business day. You understand receiving controlled substances from more than one clinician without notifying the clinicians involved is a crime (doctor shopping), and that conviction can result in a prison sentence.

2. You will fill all prescriptions for controlled substances at one pharmacy. That pharmacy and telephone number is ______________________.
You give our office permission to discuss your medications with pharmacists at this, or any other pharmacy, or with any other clinician that has treated you.

3. You understand that taking controlled substances will eventually result in physical dependence and stopping the medication suddenly could cause a withdrawal syndrome. You accept this risk. You further understand that should you have to leave the practice, we are not responsible for finding another clinician who will prescribe for you.

4. You understand that if you have a past history of alcohol or drug abuse, or a family history of these issues, you are more likely to develop problems with these medications. By signing this document, you state that you have notified us of any such history.

5. Controlled medications can be dangerous to others and may also be stolen for illicit use. You accept responsibility to store your medication safely and securely so that no one but yourself has access to it. A lockbox or safe is strongly recommended.

6. Lost, damaged, or destroyed medications cannot be replaced. Stolen medication may be replaced a single time after a police report is obtained. If your medication is stolen a second time, we consider this evidence that you are not capable of protecting your medication and we will not replace it.

7. You may not take extra medication, no matter how bad your pain is, without calling the office and receiving permission to do so BEFORE you take it. Medications cannot be refilled early.

8. Medications are only refilled weekdays between 9 am and 4 pm. No exceptions are made.

9. You understand that by undertaking your treatment, we do not guarantee that we can provide complete pain relief. You also understand that treatment which is initially effective may lose effectiveness over time. When this occurs, the clinician may or may not be able to change medications or dosages to restore effectiveness. Undertaking your treatment does not guarantee, nor do we assume responsibility for providing, continued access to medication.

10. You understand that random urine drug screens, are part of the requirements for continued treatment. You understand that insurance may not cover the cost of these screens. You understand that refusal to take a urine screen will

result in immediate dismissal from the practice, as will the presence of any unprescribed controlled substance in your urine.

11. If responsible legal authorities have reason to question your use of controlled substances, as might occur if they suspect drug diversion, you understand that we waive any clinician-patient confidentiality and provide immediate access to your medication records.

12. You understand that violating any terms of this agreement may result in your immediate dismissal from this practice. In such cases, we are not responsible for referring you to another clinician, nor are we responsible for providing further prescriptions. You understand that should a withdrawal syndrome occur in such circumstances, we will refer you to an appropriate facility for detoxification, and you are responsible for the cost of such treatment.

Signatures:

______________________ Patient	______________ Date
______________________ Family Member	______________ Date
______________________ Clinician	______________ Date

____
Patient name printed

SECTION TWO

Opioid Pharmacology

CHAPTER SEVEN

Pharmacology and Chemistry

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Explain the role of the opioid receptor.
- Describe the mechanism of action of morphine and other opioids in analgesia.
- Discuss the pharmacologic effects of morphine and other opioids.
- Describe the phenomenon of tolerance to morphine.
- Describe the phenomenon of dependence to morphine.
- Explain the basic chemistry of KADIAN®.

Terminology

Acidic:	A pH less than 7.0.
Alkaline:	A pH greater than 7.0.
Anaphylaxis:	An unusual or exaggerated allergic reaction that may be life threatening.
Antagonist:	Drug that binds to a receptor site, inhibiting its action.
Baroreceptor reflex:	A reflex response to activation of a sensory nerve terminal that is stimulated by changes in pressure. These are located in the blood vessel walls.
Endogenous:	Any substance produced within the body.
Hydrophilic:	Substance that is soluble in aqueous solution (literally translates as "water loving").
Ileus:	Paralysis (usually temporary) of the bowels, which typically leads to constipation and abdominal distention. More severe ileus can cause nausea and vomiting as well.
Lipophilic:	Substance that is soluble in fatty tissue (literally translates as "lipid loving").
Miosis:	Contraction of the pupil.
Mydriasis:	Dilation of the pupil.
Narcotic:	Sleep inducing medication
Opioid:	Natural, semi-symthetic, or synthetic analgesic substance that is a mu-receaptor agonist..
Orthostatic hypotension:	Drop in blood pressure upon standing.
Pathognomonic:	Denoting a sign or symptom that is characteristic enough of a condition that it can be used to diagnose that condition.
Peptide:	A naturally occurring compound of two or more amino acids.
pH:	A measure of whether a solution is acidic or alkaline.
Pruritus:	Itching.
Psychotomimetic:	Something that causes a feeling of depersonalization or dysphoria; producing symptoms similar to psychosis.
Sphincter of Oddi:	A circular muscle located where the common bile duct passes through the small intestine that controls the flow of bile into the intestine.
Supraspinal:	Occurring at the level of the brain.
Vasodilation:	Relaxation of the smooth muscle in the blood vessels that results in an increase in the size of blood vessels.

Introduction

The pain signal is transmitted to the brain through neurons using several different chemical neurotransmitters. Opioids can effectively block the transmission of this pain signal on its way to the brain. It is possible to stimulate the descending, pain pathways in the nervous system (*see* Chapter 1). Modifying opiodss may increase or decrease pain.

Opioids, which stimulate neurons in these descending, pain-suppressing pathways, are one of the few options available for treating pain. No class of drug provides analgesia as effectively as do the opioids.

Opioid use in pain relief is favored for several reasons:

- First, opioids do not have a ceiling effect to their efficacy.
- Second, opioids have a long history of use and demonstrated efficacy.
- Third, it is widely accepted that opioids--particularly extended-release formulations--improve the quality of life of cancer patients.

This chapter reviews the mechanism of opioid analgesia and other pharmacologic effects. Particular attention is given to morphine, the "gold standard" for pain relief.

Chronic Pain Pathophysiology

The main neurotransmitter used by nociceptors (pain transmitters) synapsing with the dorsal horn of the spinal cord is glutamate. Glutamate can bind to many receptors, but the AMPA (alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid) receptor is most involved in transmitting the acute pain signal.

Chronic pain is not a prolonged version of acute pain. As pain signals are repeatedly generated, neural pathways undergo changes that make them hypersensitive to pain signals and resistant to antinociceptive (pain blocking) input. One theory explaining the transition from acute pain to chronic pain involves NMDA (*N*-methyl-D-aspartate) receptor activation. The NMDA receptors are not active unless there has been a persistent or large-scale release of glutamate (Figure 7-1). Repeated stimulation of AMPA receptors dislodges magnesium ions that act like stoppers in transmembrane sodium and calcium channels of the NMDA receptors, thereby activating the NMDA

receptors. This change marks the transition from acute pain to chronic pain. Now, more NMDA receptors are available for glutamate to bind because they have been activated (a phenomenon called windup). It therefore takes less peripheral input for pain stimulation to occur, less glutamate to transmit the signal, and more antinociceptive input to stop it.

Ketamine, dextromethorphan, and methadone all have some NMDA receptor antagonist activity and have been used to try to stop this transition from acute pain to chronic pain and to block the activity of the activated NDMA receptors. Unfortunately, drugs that target the NMDA receptor do not provide pain relief without significant side effects. For this reason, opioid receptor agonists remain the preferred treatment for chronic pain.

Endogenous Opioid Peptides

Endogenous peptides are the primary chemical messengers in the antinociceptive system of the body. Endogenous opioids bind to receptors to produce analgesia. Endogenous opioids are composed of three distinct families of peptides, all of which are pharmacologically related to morphine:

- enkephalins,
- dynorphins, and
- endorphins.

Opioid medications, such as morphine, bind to receptors and block pain modulating systems in a similar manner to these endogenous opioids.

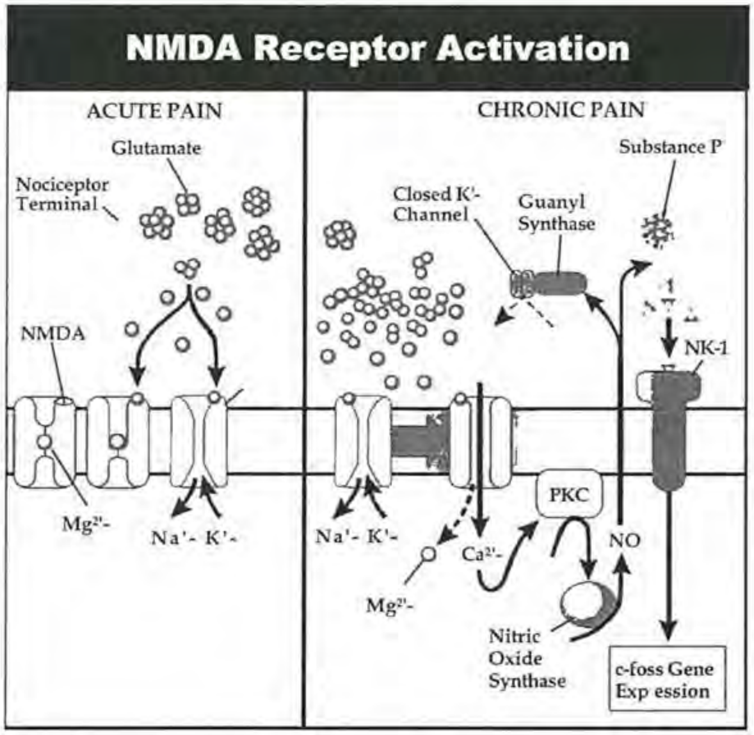


Figure 7-1

Adapted from Brookoff, 2000

Opioid Receptors

Opioids exert their effects on the body by interacting with specialized macromolecular (large molecule) components in cells called opioid receptors. Opioid receptors are located in the central nervous system (CNS), pituitary gland, the peripheral nervous system (PNS), the gastrointestinal (GI) tract, and a few other locations in the body. They are abundant in the periaqueductal gray matter of the brain and the dorsal horn of the spinal cord, two areas that are very active in pain reduction. When an opioid binds to one of these receptors as an agonist, it produces analgesia. When a drug binds to one of these receptors as an antagonist, analgesia and other effects are blocked.

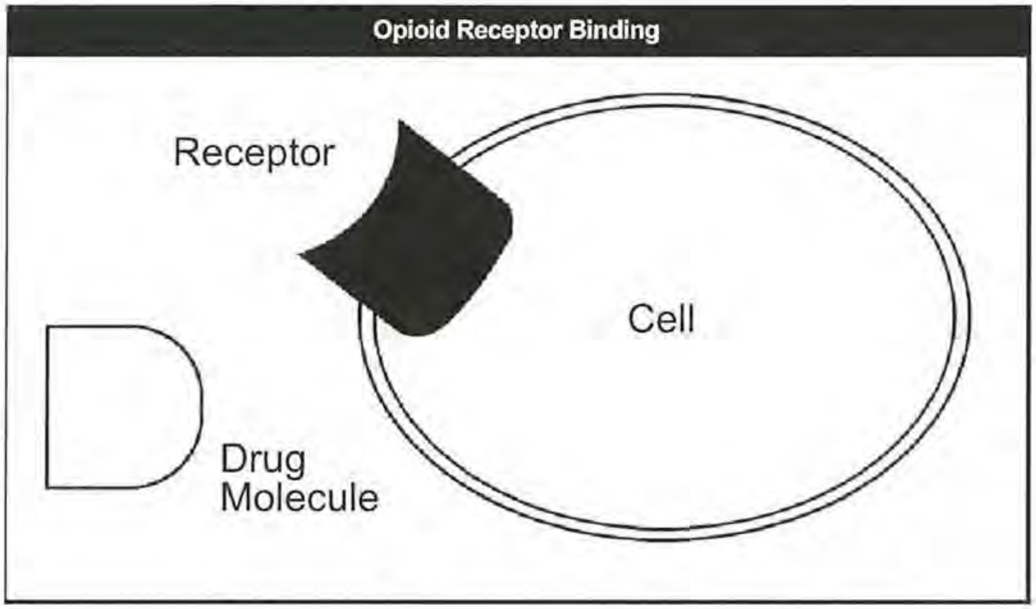
Three major types of opioid receptors are involved in analgesia:

- mu,
- kappa, and

- delta.

Many subtypes of these receptors exist. The binding of drug molecules to their specific receptors is similar to a key fitting a lock (Figure 7-2). The bond between the drug and the receptor distorts the configuration of the receptor, changing its biochemical properties and function and triggering specific responses by the cell. The body's response to the drug is a result of these changes.

Figure 7-2



Opioid Analgesics

Opioids are divided into 3 classes (Table 7-1):

Mu agonists

Most clinically useful opioid analgesics, which bind primarily to the mu (μ) receptor.

Mixed agonist-antagonists

Bind as agonists at the kappa receptor producing weak analgesia and also bind as weak antagonists at the mu receptor. The result is weak analgesia and more dysphoria and psychotomimetic effects and less intense respiratory depression than is seen with pure agonists. These drugs have very limited clinical utility.

Partial agonists

Bind as agonists at mu and kappa receptors, but have limited efficacy.

Table 7-1.

Mu agonists	Mixed agonist-antagonists	Partial agonist
Codeine Fentanyl Hydromorphone Levorphanol Meperidine Methadone Morphine Oxycodone Oxymorphone Hydrocodone	Butorphanol Dezocine Nalbuphine Pentazocine	Buprenorphine

Pharmacologic Properties

Morphine and related opioids produce their major effects on the CNS and the bowel through mu receptors. Although morphine is relatively selective for mu receptors, it can interact with the others, particularly at higher doses. The type of opioid receptor site and its location determine the effects an opioid drug produces (Table 7-2). Analgesia is a beneficial result of mu receptor binding. Side effects are unwanted results of the binding to opioid receptors.

Table 7-2

Activity of Mu, Kappa and Delta Receptors	
Opioid Receptor Site	**Activity**
Mu (μ)	Spinal and supraspinal analgesia, respiratory depression, cardiovascular effects, physical dependence, tolerance, impaired GI motility, urinary retention, pruritus, euphoria.
Kappa (κ)	Spinal and supraspinal analgesia, miosis, psychotomimetic effects (dysphoria, agitation), and sedation without pronounced respiratory depression, euphoria, or GI effects.
Delta (δ)	Spinal and supraspinal analgesia without

	respiratory compromise.

Analgesia

Analgesia is produced at mu, kappa, and delta receptors supraspinally and spinally. In the case of morphine, analgesia appears to be mediated primarily through μ (mu) receptor activation. There are two distinct subtypes of μ receptors, μ_1 and μ_2. The μ_1 receptor is responsible for morphine analgesia at the supraspinal level, whereas the μ_2 receptor mediates morphine analgesia at the level of the spinal cord. Morphine given systemically interacts with supraspinal μ_1 receptors. Both respiratory depression and constipation are thought to be mediated by μ_2 receptors.

Biliary Spasm

Opioids increase smooth muscle tone in the biliary tract, especially in the sphincter of Oddi, which regulates the flow of bile and pancreatic fluids. This can result in a decrease in biliary and pancreatic secretions and a rise in bile duct pressure. Patients may experience epigastric (upper abdominal) pain and occasionally spasm of the biliary tract, which causes pain that is similar to that experienced with a gallstone blockage of the gallbladder.

All opioids can cause constricture of the sphincter of Oddi and the biliary tract. One study showed that morphine might cause more biliary constricture than do other opioids in animals. This has not been shown to be of clinical importance in humans, however.

Cardiovascular System

Therapeutic doses of many opioids produce peripheral vasodilation, reduced peripheral resistance, and inhibition of the baroreceptor reflexes. Orthostatic hypotension and fainting can result. Morphine and other opioids provoke release of histamine, which sometimes plays a large role in hypotension.

Central Nervous System

Opioid drugs produce many CNS effects. They cause drowsiness, changes in mood, and mental clouding. Confusion, disorientation, cognitive impairment, hallucinations, and euphoria are also possible. Psychotomimetic effects are more common with kappa receptor activation.

Convulsions

High doses of morphine and related opioids produce convulsions (seizures). Most convulsions occur at doses far in excess of those required to produce analgesia.

Cough

Opioids depress the cough reflex by a direct effect on the cough reflex trigger zone in the medulla of the brain stem.

Gastrointestinal Tract

Opioid binding of mu receptors in the GI tract can delay gastric emptying, slow bowel motility, and decrease peristalsis. Opioids may also reduce secretions from the colonic mucosa. The result is slow moving, hard stool that is difficult to pass. At its worst, GI dysfunction results in ileus, fecal impaction, and obstruction.

Constipation is the most common opioid side effect and one of the few for which individuals do not develop tolerance. All patients taking "around the clock" opioid analgesics should be placed on prophylactic regimens for constipation.

Genitourinary Tract

Opioids increase smooth muscle tone in the bladder and ureters and may cause bladder spasm and the sensation of the need to void urgently. An opioid-induced increase in contraction of the bladder outlet sphincter, however, can make urination difficult. Urinary retention (inability to empty the bladder) is most common in elderly men. Tolerance to the opioid effects that lead to urinary retention develops over time.

Miosis

Morphine and most mu and kappa agonists can cause constriction of the pupil. After a toxic dose of mu agonists, miosis is marked and the resulting "pinpoint" pupils are pathognomonic; however, the miosis is replaced by mydriasis once asphyxia (inadequate oxygen supply from inadequate breathing) from respiratory depression from the toxic doses develops.

Nausea and Vomiting

Nausea and vomiting are caused by direct stimulation of the chemoreceptor trigger zone in the medulla (brainstem), sensitization of the vestibular system (needed for balance and equilibrium), and slowing of GI mobility. All clinically significant mu agonists produce some degree of nausea and vomiting.

Neuroendocrine

Morphine acts in the hypothalamus to inhibit the release of gonadotropin-releasing hormone (GnRH) and corticotrophin-releasing factor (CRF), thus decreasing levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), and endorphins. Blocking the release of these hormones from the hypothalamus leads to changes in hormones released from the endocrine glands (including the adrenal glands and gonads). In turn, this may cause decreased levels of testosterone and cortisol, disturbances in menstruation, and sexual dysfunction. Tolerance may or may not develop to the endocrine effects of opiates.

Opioid Allergy

Allergic and anaphylactic reactions are rare complications of opioid therapy. In the past 12 years, the clinical literature has carried single case reports of anaphylactic reactions to meperidine, pentazocine, morphine, and fentanyl. However, many of these reports suggested the possibility of the reactions resulting from other medications taken concurrently or from inert ingredients in the drugs formulations. None of these reports documented cross-sensitivity (an allergy to other similar agents) with other opioid analgesics. Reviews of studies involving several thousand patients receiving meperidine or morphine showed no cases of cross-sensitivity. However, if the patient has a documented "allergy" to an opioid, it may be wise to avoid drugs that are structurally similar to that opioid (Table 7-3).

Respiration

Respiratory depression is the most feared opioid-induced side effect. Opioids depress respiration by a direct effect on the brainstem respiratory centers, making the brainstem less responsive to carbon dioxide. Tolerance to the opioid effects that cause respiratory depression develops in days to weeks. The longer the patient receives opioids, the wider the margin of safety.

The agonist-antagonists were developed with the intent of decreasing the risk of respiratory depression. They have a ceiling effect (point beyond a certain dose at which further respiratory depression or analgesia is not produced), but this is usually above recommended doses.

Skin

Therapeutic doses of morphine cause dilation of cutaneous blood vessels (blood vessels in the skin). Flushing can occur on the face, neck, and upper thorax. These changes may be due in part to release of histamine and may be responsible for the sweating and some of the pruritus that occasionally follows morphine administration. Histamine release can lead to wheezing and bronchoconstriction and can trigger or worsen asthma attacks, potentially leading to status asthmaticus (a severe, life-threatening asthma attack that does not respond to usual asthmatic treatments).

These reactions are similar to an allergic reaction and can be managed with anti-histamine. However, histamine release is a pharmacologic property of the opioid and not an immune system response to an allergen (i.e., not a true allergy). The naturally occurring and semi-synthetic products are potent histamine releasers.

Table 7-3

Opioid Classification		
Opioid	Type of Product	Similar Chemical Structure
Codeine	Natural	Morphine
Fentanyl	Synthetic	Meperidine
Hydrocodone	Semi-synthetic	Morphine
Hydromorphone	Semi-synthetic	Morphine
Levorphanol	Semi-synthetic	Morphine
Meperidine	Synthetic	Meperidine
Methadone	Synthetic	Unique
Morphine	Natural	Morphine
Oxycodone	Semi-synthetic	Morphine
Oxymorphone	Semi-synthetic	Morphine
Propoxyphene	Synthetic	Morphine

Summary of the Pharmacologic Effects of Opioids

- Analgesia.
- Biliary spasm.
- Peripheral vasodilation (postural hypotension and fainting).
- CNS depression (sedation, occasionally euphoria, dysphoria).
- Convulsions.
- Suppression of the cough reflex.
- Decreased GI motility (constipation or ileus).
- Inhibition of the urine voiding reflex (urinary retention).
- Pupillary constriction (miosis).
- Stimulation of chemoreceptor trigger zone (nausea and vomiting).
- Smooth muscle contraction and spasm (constipation and reduced urine output).
- Opioid allergy
- Respiratory depression.
- Stimulation of histamine release (sweating, flushing, pruritus, red eyes, postural hypotension, wheezing or worsening of asthma symptoms).

Expected side effects of opioids are often mistaken for or mislabeled as allergies.

Addiction, Dependence, and Tolerance

Opioids often have their use limited by concerns regarding misuse, addiction, and possible diversion for nonmedical uses. An understanding of terminology is necessary for effective communication regarding tolerance, dependence, and addiction.

Addiction

Addiction is the psychological dependence on the use of substances for psychic effects and is characterized by compulsive use. Consider addiction if patients no longer have control over drug use and continue to use drugs despite harm.

Physical dependence

Physical dependence means that changes in the body's response to endogenous and exogenous opioids have developed such that a withdrawal syndrome develops after an opioid drug is stopped or quickly decreased without titration. Administration of an opioid antagonist also causes withdrawal. Warn patients to avoid abrupt discontinuation of an opioid. Many medications produce dependence. These include: opioids, sedatives, stimulants, anxiolytics, muscle relaxants, beta blockers, and antidepressants.

> *The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine recognize the following definitions and recommend their use.*
>
> **Tolerance**
>
> Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.
>
> **Physical Dependence**
>
> Physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.
>
> **Addiction**
>
> Addiction is a primary, chronic neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.
>
> AAPM, APS, ASAM 2001

Pseudoaddiction

Pseudoaddiction is drug-seeking behavior that seems similar to addiction but is due to unrelieved pain. This behavior stops once the pain is relieved, often through an increase in opioid dose.

Pseudotolerance

Pseudotolerance is the need for an increase in dosage that is not due to tolerance, but is due to other factors, such as disease progression, new disease, increased physical activity, lack of compliance, change in medication, drug interaction, addiction, and deviant behavior.

Tolerance to Analgesic Effects

Tolerance to analgesia is the need for an increased dosage of a drug to produce the same level of analgesia. Tolerance develops to analgesia more slowly than to other opioid effects. Analgesic tolerance does not occur in every patient and is not addiction.

Tolerance to morphine is both **dose**-and **time-dependent.** Large doses of morphine given over a short period will be associated with a more rapid development of tolerance. Conversely, tolerance develops less rapidly when small doses are given. This observation is based on animal studies and its relevance to humans is unclear. In addition, great individual variation exists in the development of tolerance.

Tolerance to Side Effects

Tolerance develops to most of the adverse effects of opioids after 2 to 3 weeks of continuous administration. Tolerance to the constipating effects of opioids does not develop.

Morphine Pharmacology

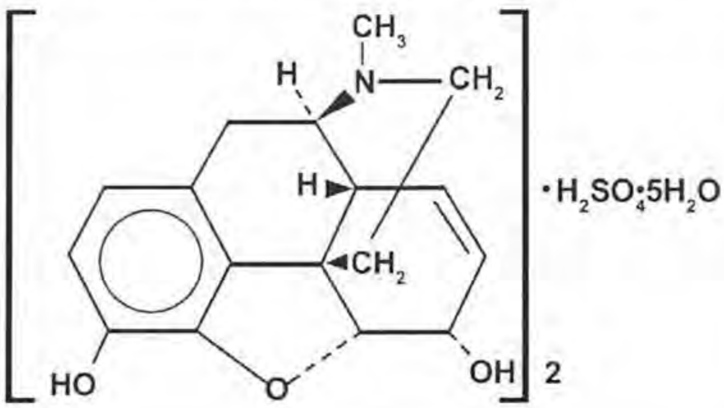
Despite the availability of several newer opioids, morphine remains the prototype opiate analgesic. As new opioid compounds are developed, their efficacy and side-effect profiles are compared with those of morphine. Morphine is a naturally occurring alkaloid derived from opium, the dried sap of the unripe fruit capsule of the poppy plant (*Papaver somniferum*). Its analgesic activity has been recognized for more than 3000 years.

Morphine is given either as the hydrochloride or sulfate salt, and these are regarded as interchangeable. The chemical structure of morphine sulfate is shown in Figure 7-3. Morphine sulfate is an odorless, white crystalline powder with a bitter taste. The bitter taste means the drug is unpalatable in liquid formulation, a drawback that can be avoided with a capsule or tablet formulation. Morphine sulfate is highly soluble in water and alcohol but is practically insoluble in chloroform and ether. Its high solubility has provided the challenge in formulating a extended-release product.

Typically, morphine is given orally (PO), intravenously (IV), subcutaneously (SC), and intramuscularly (IM). It may also be given by sublingual, rectal, epidural, and intrathecal (into the spinal fluid) routes.

Figure 7-3

Chemical Structure of Morphine Sulfate



KADIAN® PHARMACOLOGY

KADIAN® is a extended-release formulation of oral morphine sulfate presented as polymer-coated pellets in a gelatin capsule. It provides effective pain management (or similar pain control) with fewer doses of morphine than are normally required with conventional immediate-release formulations. KADIAN® capsules are formulated in five strengths containing 20, 30, 50, 60, or 100mg of morphine sulfate plus inactive ingredients.

KADIAN® Pellet Technology

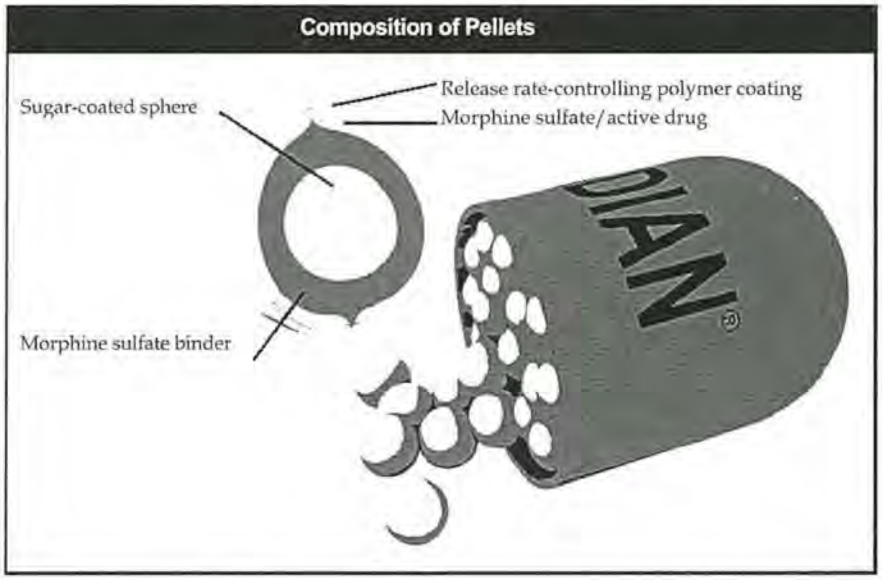
The KADIAN® capsules consist of a hard gelatin shell containing polymer-coated morphine sulfate pellets. The release of morphine from the pellets is pH dependent, with the rate of release increasing as the pH of the medium around the pellet increases.

After ingestion, the gelatin capsule dissolves in the stomach and the pellets are released. In the strongly acidic medium of the stomach, morphine release from the pellets is minimal. As the pellets pass into the more alkaline small intestine, the rate of release increases substantially. Release of morphine increases as the pellet passes through the small intestine into the large intestine, with the rate of release increasing as the pH becomes more alkaline. The pellets are designed to release morphine for up to 24 hours. This is the basis for once-a-day administration of KADIAN®.

Composition of Pellets

Each pellet has essentially four layers. The first layer is the release rate-controlling polymer coating. This coating consists of ethylcellulose, polyethylene glycol, and methacrylic acid. The second layer is the morphine sulfate or active drug. The third layer is a substance that binds the morphine to the inner core of the sphere. The core or the fourth layer is a sugar-coated sphere.

Figure 7-4: Composition of Kadian® capsule



- Ethylcellulose: a strong, insoluble component that forms the mechanical basis of the coating.
- Polyethylene Glycol: a water soluble, pH-independent component that bestows permeability at all pH levels.
- Methacrylic Acid: water soluble, pH-dependent component that bestows additional permeability at pH levels above 5.5 to 6.0.

At gastric pH, the polyethylene glycol component dissolves, forming pores through which the morphine may diffuse outward. These pores are relatively small, allowing only limited diffusion. At intestinal pH levels of 5.5 and higher, both the polyethylene glycol and the methacrylic acid dissolve. The size of the pores in the methacrylic acid is directly proportional to the pH of the surrounding fluids; the higher the pH, the larger the pore. Thus, most of the morphine release occurs through the pores in the methacrylic acid component of the polymer coating.

The ethylcellulose component of the capsule is insoluble. Therefore, remnants of the pellets may be evident as white or opaque spheres in the feces of patients treated with KADIAN®.

Summary

- Morphine has a wide range of pharmacologic actions in addition to analgesia, many of which result in unwanted side effects. The effects of morphine on the CNS include depression, stimulation, nausea and vomiting, depression of the cough reflex, and miosis. Through its direct inhibitory action on the brainstem respiratory centers, morphine also acts as a powerful respiratory depressant. Morphine also may cause orthostatic hypotension, constipation, reduced urinary output, and disturbances of menstruation and libido. Finally, morphine increases blood flow to the skin and stimulates histamine release, causing variable degrees of sweating, flushing, and pruritus and may cause wheezing or worsening of asthma symptoms.
- Patients receiving morphine for long periods often develop dose- and time-dependent tolerance to the drug's effects on the CNS. Minimal tolerance occurs to the constipating effects of morphine and patients need to continue appropriate treatment. In patients with cancer pain, tolerance to the analgesic effects of morphine is rarely the reason that dosage increases are required; rather, the patient is usually experiencing an increase in pain severity as a result of cancer or disease progression.
- Patients using opioid analgesics may continuously develop a physical dependence with or without a psychological dependence.
- KADIAN® is a unique dosage formulation that provides analgesia for up to 24 hours when dosed Q12 or Q24 hrs. It provides effective pain management with fewer doses of morphine than are normally required with conventional formulations.

Literature Cited

- Brookoff D. Chronic Pain: The Case for Opioids. Hospital Practice. 2000;69-84.

Self-Assessment Test

Circle the best response

1). Patients using opioid analgesics continuously can expect to develop - ________________.
 a. Addiction
 b. Physical dependence
 c. Pseudotolerance
 d. Psychological dependence

2). Which of the following is a side effect of morphine sulfate?
 a. Hypertension
 b. Nausea
 c. Mitosis
 d. Cough

3). Histamine release is a pharmacologic property of opioids and results in all of the following except:
 a. Pruritus
 b. Sweating
 c. Flushing
 d. Allergic reactions

4). Which of the following is true regarding the composition of KADIAN® capsules?
 a. A KADIAN® pellet consists of 5 layers.
 b. The methacrylic acid of the polymer layer is permeable at all pH levels.
 c. The polymer layer is rate controlling.
 d. The size of the pores in the polyethylene glycol layer is directly proportional to the pH of the surrounding fluids.

True or False

5). Morphine and related opioids produce their major effects on the CNS and the bowel through mu receptors.
 a. True
 b. False

6). Opioid receptors are located in the CNS, pituitary gland, GI tract, and spinal cord.
 a. True
 b. False

7). Psychotomimetic effects are more common with the kappa receptor agonist activity.
 a. True
 b. False

8). The rate of release of morphine from KADIAN® increases as the pH becomes more acidic.
 a. True
 b. False

9). Analgesic tolerance is an expected result of chronic opioid therapy.
 a. True
 b. False

10). Tolerance to constipation develops in 1 to 2 weeks.
 a. True
 b. False

11). KADIAN® provides analgesia for up to 24 hours.
 a. True
 b. False

Answers to Self-Assessment Test

1. b	7. a
2. b	8. b
3. d	9. b
4. c	10. b
5. a	11. a
6. a	

CHAPTER EIGHT

Pharmacokinetics

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the types of modified-release morphine preparations.
- Describe the mechanism of morphine release in KADIAN® capsules.
- Describe the absorption of morphine from KADIAN® capsules.
- Describe the bioavailability of morphine from KADIAN® capsules.
- Describe the major findings of the single-dose KADIAN® research.
- Describe the major findings of the steady state KADIAN® research.
- Describe the pharmacokinetics of KADIAN®.
- Discuss the metabolism and excretion of KADIAN® and the clinical implications.

Terminology

AUC:	Area under the curve. Graphically, this is the area under a drug's absorption curve. It represents the amount of drug absorbed after a dose.
Bile:	A greenish-yellow bitter fluid produced in the liver and stored in the gallbladder. Bile that flows in bile ducts from the gallbladder to the intestine helps in the digestion and absorption of fat.
Bioavailability:	The degree to which a drug or other substance becomes available to the target tissue after administration.
C_{max}:	Maximum concentration in the blood of a drug after dosing.
C_{min}:	Minimum concentration in the blood of a drug after dosing.
Clearance:	A measure of the body's ability to eliminate a drug from the body.
Conjugation:	A reaction that joins a drug with another molecule to produce a form that can be eliminated by the kidney.
Delayed release:	A drug formulation that delays the release of a drug until it has passed out of the stomach and into the intestine.
Delayed gastric emptying:	Slow transit of stomach contents out and into the intestine. This can result from drug side effects or disease states.
Extended-release:	A drug formulation that releases the drug over an extended period of time.
First-pass metabolism:	Metabolism of a drug that occurs during its first passage through the liver in the circulation, right after absorption from the intestine.
Half-life $(t_{1/2})$:	Time required for an organism to eliminate one-half of a substance that has been introduced into it.
Hyperalgesia:	Abnormal sensitivity that causes normal sensations to be interpreted as pain and painful sensations to be more intense.
Linear pharmacokinetics:	Having absorption and elimination properties that lead to a proportional relation between dosing and serum drug concentrations.
Lipophilic:	lipid soluble
Metabolite:	a product of metabolism. A byproduct of a drug that has undergone chemical changes due to biochemical processes in the body.
Metabolism:	The interactions of a drug with the body's biochemical processes. It usually results in a drug's structure and properties changing. The physical and chemical processes essential for an organism to live, and also the transformation by which energy is made available for the use by the organism.
Morphine-3-glucuronide (M3G): The predominant metabolite of morphine that has opioid antagonistic effects.	
Morphine-6-glucuronide (M6G): A metabolite of morphine that has analgesic properties.	

Myoclonus:	Spasmodic skeletal muscle twitches.
Nonlinear pharmacokinetics:	Having absorption and elimination properties that lead to a nonproportional relation between dosing and serum drug concentrations. This means that responses to changes in doses are more difficult to predict.
Pharmacokinetics:	A branch of pharmacology dedicated to the determination of the fate of substances (primarily drugs) administered to a living organism (usually humans). The term is derived from the greek words "pharmacon" (meaning drug) and "kinetikos" (meaning putting in motion).
Phase I reactions:	One set of enzymatic processes in the liver that metabolize drugs. Phase I reactions include oxidation, hydrolysis, and reduction.
Phase II reactions:	One set of enzymatic processes in the liver that metabolize drugs. Phase II reactions include conjugation to form glucuronides, acetates, or sulfates.
Protein-binding:	The property of drugs that causes them to adhere to proteins in the serum.
Steady state:	Condition of dynamic equilibrium between administration and elimination of a drug.
t_{max}:	Time required to achieve maximum plasma concentration of a drug.
US Pharmacopoeia:	A legally recognized compendium of standards for drugs. It includes assays and tests for determination of strength, quality, and purity.
Volume of distribution:	A measure that describes the concentration of drug in the body tissues.

Introduction

After systemic administration, an opioid drug is absorbed into the vascular system. For the drug to produce a pharmacologic effect, it must leave the plasma, diffuse into the tissues, reach the opioid receptors, and activate them. Appropriate use of opioid analgesics requires an understanding of these pharmacologic concepts. This chapter will review the dynamics of drug absorption, distribution, metabolism, and elimination of opioids. In addition, the chapter discusses the pharmacokinetics of KADIAN®, and how these data must be integrated into clinical utilization.

General Pharmacokinetic Principles

Pharmacokinetics is the study of the absorption, distribution, metabolism, and elimination of a drug.

Absorption

Absorption describes how fast and how much of a drug leaves its site of administration (oral, parenteral, rectal). The speed and degree to which a drug is absorbed is important, although ultimately bioavailability of the drug determines to what degree a drug reaches its intended site of action.

Absorption is influenced by many factors. The larger surface area of the intestine, combined with its improved absorption properties, leads to better absorption of drugs in the intestine than the stomach. Thus, drugs that leave the stomach quickly are likely to be absorbed more quickly. Anything that delays stomach emptying may reduce or delay absorption of the drug. Drugs that are strong bases (high pH) or strong acids (low pH) do not diffuse easily into cells and therefore are absorbed poorly. Some drugs are destroyed by stomach acid and require administration in a form that has been engineered to protect it from stomach acid or it must be given by a nonoral route.

A drug that is absorbed very quickly causes a rapid rise (and then usually a rapid decline) in serum drug concentrations. A drug that is absorbed slowly leads to drug concentrations that have a lower peak; because they are absorbed over a longer time, they are present in the serum for a longer period of time. A rapid rise in serum concentrations is useful to obtain a rapid onset of action, but can lead to toxicity at the

peak concentrations and the benefits of the drug may wear off quickly. A slower rise in serum concentrations leads to a slower onset of action, but may avoid toxicity of the rapid high peak concentrations seen with faster absorption rates and provide a longer duration of action (See Figure 8-1). Strategies that take advantages of these effects are used in formulating drugs and determining dosages.

For some drugs that have slow absorption, a loading dose (a large initial dose) may be given to speed the time until a therapeutic blood concentration of the drug is reached. A maintenance dose, which is a lower dose than the loading dose, is then given to maintain the blood concentration of the drug at the desired level.

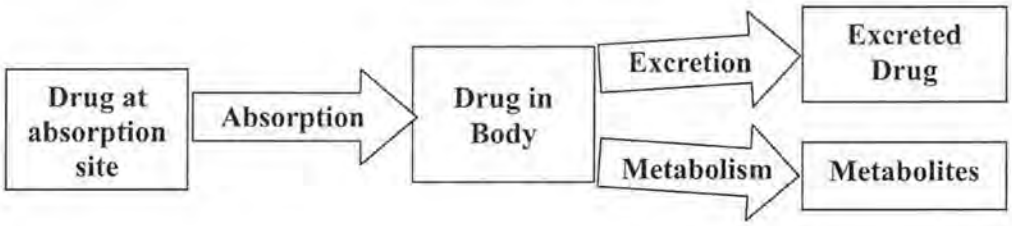
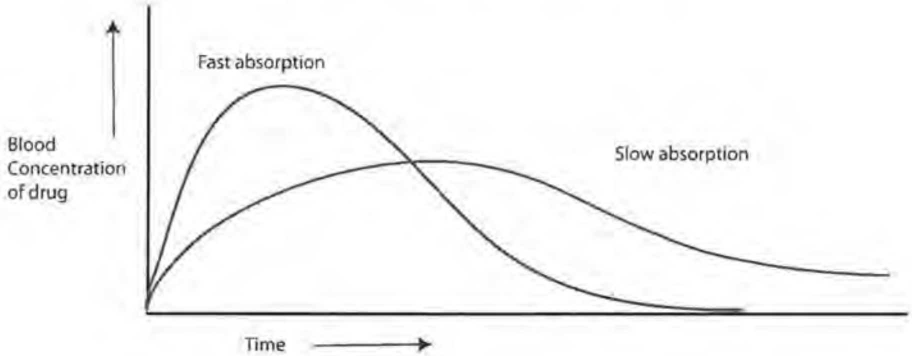


Figure 8-1: Absorption profiles



Food

Food may change the rate of absorption of many medications, usually because of the delayed gastric emptying associated with eating. This does not always mean the total

amount of drug absorbed changes; the drug may simply be absorbed more slowly. In some cases, however, the nutrients in food may actually bind medications and prevent absorption, reducing the amount of drug absorbed. For example, many drugs bind to calcium and once bound cannot be absorbed. These drugs cannot be taken with dairy products or calcium-based antacids or they will not be absorbed.

Drug Formulation

To have the desired effect, a drug must reach the site of action in an adequate quantity. There are numerous factors that affect absorption and distribution of different drugs. The properties of absorption and distribution are taken into account as the delivery form of the drug is designed so that the formulation allows the drug to be delivered to the site of action in the amount and frequency needed.

The rate of absorption of an oral drug is partly dependent upon the rate it dissolves in the gastrointestinal fluids. This factor is the basis for the so-called long-acting pharmaceutical preparations that are designed to produce a slow, uniform absorption of the drug for 8 hours or longer. Advantages of such a preparation are a reduction in the frequency of administration and maintenance of a therapeutic effect overnight. In addition, elimination of peaks in the drug concentration that occur after administration of an immediate-release dosage results in a decreased incidence or intensity of undesired effects.

The US Pharmacopoeia recognizes and defines two types of modified-release dosage forms: extended-release and delayed-release. A modified-release dosage form is a dosage form in which the rate or site of release of the active ingredients in the gastrointestinal tract has been modified.

Extended-Release

An extended-release formulation releases a drug over an extended period. This allows a reduction in dosing frequency compared with a drug presented in a conventional dosage form. Various strategies are used to control the release of a drug. For example, coatings may be placed around small amounts of drugs to produce small beads. The drug is released as the coatings dissolve. The coatings may be designed to dissolve in stomach acid (very low pH) or may be impervious to acid but dissolve in the relatively high pH of the intestine. Another example is the use of a skin patch,

which bypasses the issues of gastrointestinal absorption by taking advantage of the slow diffusion of drug into the skin layers.

Other terms used to describe these dosage formulations include *sustained-release*, *prolonged-action*, and *controlled-release*.

Delayed-Release

A delayed-release dosage form is one that delays the release of a drug until it has passed through the stomach. According to the US Pharmacopoeia, enteric-coated dosage forms are delayed-release dosage forms. Many of these drugs have coatings or packaging that is resistant to stomach acid but that is affected by the high pH of the intestine.

This manual has adopted the following classifications:

Conventional: Conventional refers to solutions or immediate-release oral dosage forms from which the total dose is immediately available.

Extended-release/controlled-release/sustained-release: In practice, these terms are used interchangeably. To separate the agents for the purposes of this manual, we will refer to KADIAN® as an extended-release formulation because it has a longer duration of action than most other oral agents. MS Contin®[1] and OxyContin®[1] are referred to as controlled-release formulations since their duration of action is somewhat shorter. However, remember that outside of this manual, these terms are used interchangeably in some cases.

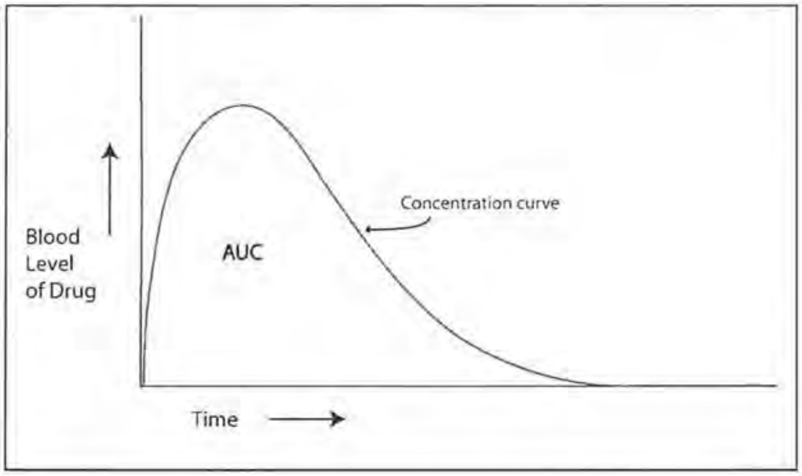
Bioavailability

Bioavailability is the extent to which a drug reaches its site of action. Factors that affect absorption of a drug affect its bioavailability. If a drug cannot be absorbed or is prevented from reaching its site of action, it is not bioavailable. For example, if a drug is destroyed by stomach acid, it is not bioavailable.

Mathematical descriptions of bioavailability are used to communicate various aspects of absorption and distribution of a drug in the body. The area under the curve (AUC), concentration, maximum concentration, minimum concentration, and time to reach concentration all are used to describe the extent to which the drug is absorbed (See Figure 8-1). The AUC is based on the absorption curve of a drug as determined under

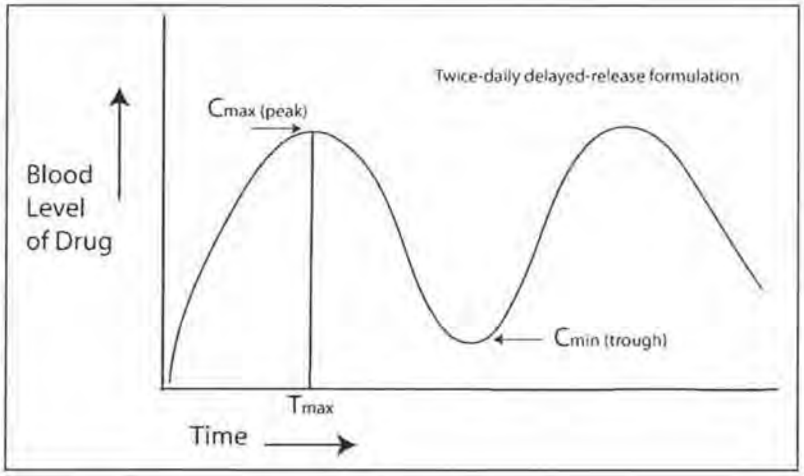
experimental conditions. In Figure 8-2, a rapid absorption curve is used to illustrate the AUC. The gray area represents the concentration of the drug in the circulation over time. In a perfect absorption state, the amount of drug represented by the entire gray area would equal the amount of the full dose given to the patient. In reality, any amount of drug that is not bioavailable (e.g., not absorbed) would not end up in the serum and would not be represented by the gray area.

Figure 8-2: Illustration of AUC



The maximum concentration (C_{max}) in the serum is the point at which the most drug is in the serum after a dose is given. That is represented by the highest point on the concentration curve. The minimum concentration (C_{min}) is the point at which the least drug is in the serum after a dose is absorbed. That is represented by the lowest point on the concentration curve. The time it takes to reach the maximum concentration (the peak) is designated as the t_{max}. (See Figure 8-3).

Figure 8-3: Biphasic blood level concentration peaks with delayed-release formulations



Factors that affect bioavailability

Several factors uniquely affect the bioavailability and the therapeutic effects of opioids. Route of administration, presence of disease states, and drug solubility are just a few of these many factors.

Route of Administration

Drugs can be delivered by different routes of administration, including intravenous, subcutaneous, intramuscular, and oral. The choice of administration route is dictated by the properties of the drug. For example, when given intravenously, a drug typically acts quickly and wears off quickly, which may or may not be desirable given the circumstances. Thus, the absorption, distribution, and elimination properties of a drug affect the decision to choose an oral or parenteral route of administration.

The oral route of administration is the most convenient and economical way to administer a drug. In addition, the drug formulation can usually be designed to control the rate of release of the drug, which, in turn, influences the absorption and serum concentrations of the drug. Not all drugs can be given orally; some drugs are destroyed by stomach acid, some have chemical properties that cause them to be poorly absorbed, others are too quickly metabolized by the first-pass effect. Nutrients and drugs absorbed from the gastrointestinal tract enter the blood at a point in the circulation where it is directed immediately through the liver. Drugs that are inactivated in the liver might therefore be rendered inactive before they even reach

the circulation. If the drug cannot be altered chemically to prevent this effect, it cannot be given orally because it will not be effective (i.e., it will not be bioavailable).

Opioids are 100% bioavailable when given intravenously because they are introduced directly into the systemic circulation. When administered orally, opioids are absorbed from the gastrointestinal tract and are transported by the portal vein to the liver, the primary site of drug metabolism. Bioavailability depends on how much of the drug is absorbed in the gastrointestinal tract and how much is inactivated as it passes through the liver. Bioavailability decreases if the liver has a great capacity to metabolize and excrete the drug. When morphine is given intravenously it has 100% bioavailability, and the recommended dose in severe pain is 10 mg. When given orally, which subjects the drug to significant liver metabolism and first-pass effect, the equivalent dose is 3 times as great
(30 mg).

Disease States

The presence of a pathologic condition also affects bioavailability. For a drug that is inactivated in the liver, bioavailability increases in patients with liver disease because the liver cannot metabolize (inactivate) and excrete the drug efficiently. For drugs that have to be metabolized to an active form before they are bioavailable, impaired liver function means that bioavailability decreases because less of the active form of the drug is available. (*See* discussion on Metabolism). In patients with kidney disease, drugs that are normally removed from the body by the kidney stay in the circulation. If doses are repeated, the drug concentrations build up, leading to increased bioavailability (and toxicity).

Drug Solubility

The lipid layer of a cell's membrane serves as a boundary that drugs must cross to reach the systemic circulation. The more lipid soluble (also called lipophilic, meaning readily dissolved into fatty tissue) the drug, the more readily it moves through membranes; thus, the faster and greater the absorption. Drugs that have strong electrical charges on them (have a high or low pH) cannot cross the lipid layer as easily as drugs with a neutral electrical charge (pH-neutral drugs). For example, fentanyl is highly lipid soluble and therefore is readily absorbed into the central nervous system (CNS). Morphine is less lipid soluble than fentanyl and therefore crosses into the CNS more slowly. Because of the same lipid solubility characteristics, fentanyl diffuses back out of the CNS quickly and morphine stays in

longer. Clinically, this means that fentanyl has a more rapid onset but wears off more quickly than morphine.

Distribution

After a drug reaches the bloodstream, it is carried throughout the body and distributes throughout the various fluids and tissues. A drug may also distribute across the placenta and into breast milk. Drug molecules will enter cells, dissolve in the plasma, bind to various proteins, and absorb into fats. Each individual drug will distribute in slightly different concentrations in various parts of the body with large amounts in certain parts of the body, and smaller amounts in other areas or tissues. Eventually, the drug reaches equilibrium, meaning it has distributed throughout the tissues.

Both rate and extent of distribution are determined by how well each tissue is perfused with blood, tissue size, binding of drug to plasma proteins and tissue components, and permeability of tissue membranes.

Volume of Distribution

The volume of distribution (V_d) is a measure that describes the concentration of drug in the body tissues (as related to the amount of drug in the plasma). The volume does not refer to an actual amount of body fluid, but rather describes the fluid volume that would be required to contain all of the drug in the body at the same concentration that is in the blood. The distribution of a drug is affected by the lipid solubility of the drug, the amount of the drug that binds to proteins in the blood (*see* discussion on Protein Binding), and how easily a drug can get into different types of tissues in the body (e.g., it is harder for drugs to diffuse into the cornea from the serum). Once enough of the drug has left the bloodstream to saturate the tissues, it is possible to determine how much of the drug was diluted in the body by calculation. Thus, the volume of distribution measures the extent of the dilution of the drug into different organs and tissues.

The volume of distribution (V_d) can be calculated by a formula:

$$V_d = \text{Amount of drug in body/concentration of drug in the plasma}$$

The V_d is useful in estimating the plasma concentration when a known drug is in the body, or conversely, in estimating the dose required to achieve a given plasma drug concentration. The amount of drug in the body can be estimated by mathematical formulas that use total body fluid volume or use a modified volume estimate if it is

known that the drug does not diffuse into some areas very readily. The calculation also depends on the rate of elimination of a drug from the tissues and the distribution half-life of the drug. The distribution half-life ($t_{1/2}$) is the time it takes for the drug to be reduced by 50%. This measure reflects the time necessary for a drug to move from blood and plasma to reach equilibrium with body tissues.

Protein Binding

Many drugs are bound to plasma proteins, primarily albumin. For most drugs, the binding is reversible and depends on the concentration of the drug in the blood, the presence of other chemicals that bind to the proteins, and the strength of the binding between the drug and the protein. Many drugs bind to proteins in the blood and these reactions are not selective. As a result, different drugs will "compete" for binding to the proteins. If a drug that is highly protein-bound is no longer able to bind to proteins (because of competition with other drugs or because an abnormally low amount of protein is available), a high amount of unbound drug will be present in the serum.

Plasma protein binding limits a drug's concentration in tissues and at its site of action because only unbound drug is pharmacologically active. Thus, if binding occurs at a higher rate than expected, the drug will be less bioavailable than expected and vice versa. Plasma protein binding also affects the body's ability to eliminate the drug. For example, a drug that normally is eliminated through the kidneys by diffusion may not be eliminated because it is bound to a large protein molecule that is too large to diffuse out through the kidney glomerular filtration system. If a patient is taking a highly protein-bound drug and then begins taking a second highly protein-bound drug, the first drug will have competition for binding sites and the blood concentrations of unbound drug (active drug) will rise, which can lead to toxicity.

Many disease states and other factors influence the concentration of proteins altering the amount of bound (inactive) drug. Protein deficiency, kidney disease that causes loss of proteins through damaged glomerular membranes, and diseases that cause excessive protein formation or degradation can all cause alterations in protein binding and therefore influence the amount of unbound (active) drug that is available.

Metabolism

When a drug passes through the liver, it is subjected to multiple processes and reactions (metabolism) that change part of the drug into different compounds. Drug metabolism usually occurs in the liver through one or both of the two types of

reactions. Phase I reactions generally make the drug molecule more water soluble so that it is prone to elimination by the kidney. Phase I reactions include oxidation, hydrolysis, and reduction. Cytochrome P450 enzymes are responsible for many Phase I reactions. The metabolic reactions usually inactivate drugs, although in some cases the metabolic changes produce active metabolites. (*See* appendix 11-2 for more information on the cytochrome P450 system.)

Phase II reactions in the liver involve conjugation to form glucuronides, acetates, or sulfates. Morphine is conjugated to an active metabolite that is even more active than morphine itself.

First-pass metabolism

Nutrients and drugs that are absorbed from the intestine enter the circulation at a point that takes them directly to the liver before going on to the general circulation. Drugs that undergo significant metabolism in the liver will then be changed before they reach the rest of the body. If a drug is partially or completely deactivated by this transport through the liver, the drug will have reduced or no efficacy. The liver metabolizes a significant portion of an orally administered opioid before it ever reaches the systemic circulation. This effect does not occur if a drug is given by injection or intravenous infusion. Thus, doses given by mouth must be much larger than doses given intravenously or by injection, because the oral doses will be partly deactivated during the transit through the liver.

Elimination

Elimination occurs by excretion and metabolism. Drugs are eliminated from the body either unchanged or as metabolites. The kidney is the primary organ for elimination of both unchanged drugs and metabolites. Drugs are also excreted in the feces, breast milk, sweat, saliva, tears, hair, and skin.

Clearance

Clearance (CL) is a measure of the body's ability to eliminate a drug from the body. This is a critical concept in the administration of long-acting drugs, because the rate of elimination affects how much total drug remains in the body before the next dose is given. If a drug is inadequately cleared or is cleared less than anticipated, the next dose of the drug may lead to toxic concentrations of drug in the blood. A steady state, in which elimination is balanced against intake to achieve a desirable blood

concentration of the drug, is the ultimate goal (*see* discussion on Steady State Concentration).

Clearance is expressed as volume cleared over time, because it represents the amount of blood cleared of the drug per unit of time.

The rate of clearance for a particular drug is usually constant, rather than dependent on the size of the dose. However, clearance rates are affected by other variables, because clearance depends on the efficiency of the kidney or liver and blood flow through the organs. Clearance changes with age, sex, disease, and body composition. If clearance is reduced, the half-life (and therefore duration of action of the drug) will be prolonged. In disease states
that increase clearance, such as dialysis, the duration of action of the drug will be shortened.

Half-life

The terminal half-life ($t_{1/2}$) provides an estimate of how fast a drug leaves the body (rate of clearance). The terminal half-life is usually simply referred to as *half-life* ($t_{1/2}$). By definition, the half-life is the time it takes for the concentration of a drug in the body to be reduced by half (50%). The half-life is a simple way to represent a process that over the course of time may be complex. For example, elimination of a diuretic may be faster at first because urine flow is fast, but then as a patient gets relatively dehydrated and fluid flows more slowly through the kidney, the clearance slows. Thus, if you checked a rate of clearance early, it appears faster than if you check the rate of clearance later. Having a standardized point (the 50% concentration point) that is chosen to represent the rate makes it easier to compare drugs and elimination or absorption rates.

If a drug has a long half-life, it cannot be dosed as often as a drug with a short half-life. The drug with a long-half life would build up to toxic concentrations if it was dosed as frequently as a drug with a short half-life. Also, as clearance decreases, the half-life increases, because more of the drug remains in the body. In turn, if clearance is increased (by any means), the half-life decreases.

The half-life varies from one drug to another. For example, the half-life of morphine is 2 to 4 hours, whereas the half-life of levorphanol is 12 to 15 hours. It should be remembered, however, that the quoted half-life of a drug reflects an average half-life

in healthy persons studied in experimental conditions. Any given individual may have a slightly shorter or longer half-life than average.

Steady State Concentration

Steady state concentration (C_{ss}) occurs when the concentration of free drug is the same on both sides of a membrane (such as the capillary membrane that separates blood and tissue). This occurs when the rate of elimination of a drug equals the rate at which the drug enters the system. This is a dynamic process that is dependent on the sum of all the pharmacokinetic principles: absorption, metabolism, distribution, and excretion.

A steady state is desirable because it makes responses to doses predictable. If a steady state is not reached because more drug is being absorbed than eliminated (as occurs right after a dose is taken), then more drug effect can be anticipated. For example, if a patient takes a rapid-acting morphine tablet when he begins experiencing pain, he anticipates that the rapid rise in the serum concentrations will lead to less pain than he currently has, but he will also experience the other side effects of morphine. There is also no steady state as the drug wears off (more is eliminated than is absorbed), so the patient can anticipate return of pain and a decrease of side effects. An ideal situation is one in which the amount of drug taken in is balanced against the clearance of the drug such that the total level of drug in the blood stays relatively constant. In that ideal situation, the patient always has enough drug in his system to control his pain and yet never so much that it causes critical side effects. In other words, he is not constantly going through phases where the blood concentrations are rapidly increasing or decreasing, rather, the concentrations are steady.

Long-term opioid analgesic treatment is designed to maintain a steady state of opioid within the therapeutic range. The half-life is used to estimate how long it will take an opioid drug to reach steady state. This estimate can be used to decide how often to dose a drug in an attempt to reach the ideal steady state concentration. The full effects of a change in an opioid dose will not occur until the patient has taken the new dose for a time equal to 4 or 5 half lives, because that is how long it takes for state of balance between absorption and elimination to be reached.

Pharmacokinetics of Morphine

Absorption/Bioavailability

After oral administration, morphine is rapidly and completely absorbed from the gastrointestinal tract. Fifty percent of oral immediate release morphine solution reaches the systemic circulation in 30 minutes. Morphine is also readily absorbed after subcutaneous or intramuscular injection. The oral bioavailability of morphine varies considerably between individuals and because morphine undergoes considerable first-pass metabolism in the liver (see Metabolism), the bioavailable amount of drug normally ranges from about 20% to 40% of the oral dose taken. Because morphine given intravenously or by injection does not undergo first-pass metabolism, much more of a dose is bioavailable and therefore smaller total doses are given.

Distribution

Morphine is extensively distributed throughout the body. It is distributed to skeletal muscle, kidneys, liver, intestinal tract, lung, spleen, and brain. It also crosses the placenta and appears in breast milk. When compared with other opioids, morphine is relatively insoluble in lipids, which means that, in adults, only small amounts of the drug cross the blood-brain barrier (i.e., penetrate the brain and the cerebrospinal fluid that circulates around the brain and spinal cord). Morphine does not accumulate in tissues when given in normal doses, and therefore does not cause increasing toxicity with frequent dosing.

Morphine is not highly protein bound. Of the morphine that remains in the blood after first-pass metabolism in the liver (or that is given intravenously), only a relatively low proportion (30% to 35%) is reversibly bound to plasma proteins. The remainder is in a free form and hence is pharmacologically active. Certain disease states or concomitant drug therapy, which might displace morphine from its plasma protein binding sites, would not be expected to influence plasma concentrations of free morphine to any appreciable extent because much of the drug is already not protein bound.

Metabolism

Morphine is primarily metabolized by conjugation during first pass through the liver. Conjugation is a reaction that joins the morphine with another molecule into a form

that can be eliminated by the kidney. Conjugation in the liver is done by combining morphine with either D-glucuronic acid (called *glucuronidation*) or sulfuric acid.

Approximately 50% of morphine undergoes conjugation with D-glucuronic acid to morphine-3-glucuronide (M3G) and 5% to 15% forms morphine-6-glucuronide (M6G). Conjugation with sulfuric acid produces morphine-3-etheral sulfate, but this accounts for a small fraction of the metabolized morphine. Other minor metabolic pathways include the formation of normorphine and morphine-3, 6-diglucuronide (metabolized in the brain and kidneys rather than in the liver).

Role of morphine metabolites

M3G occurs in plasma at about 10 times the concentration of morphine after intravenous administration and at about 20 times the concentration of morphine after oral administration. For many years, M3G was believed to be pharmacologically inactive. However, animal studies suggest that it can penetrate the blood brain barrier and once in the CNS, can exert CNS excitatory effects and analgesic antagonistic effects (i.e., counteracts the analgesic opioid effect). In laboratory studies, M3G was shown to antagonize both the respiratory depression and the analgesic effects of M6G and morphine.

The next most abundant metabolite, M6G, is found in plasma in concentrations at least as great as those of morphine itself. The pharmacologic effects of morphine (both analgesia and side effects) are due in part to M6G. With single doses, the concentrations of M6G remain low, and morphine remains the major active analgesic agent. However, chronic oral dosing of morphine leads to accumulation of M6G to concentrations in the blood that are greater than those of morphine. Since M6G has analgesic effects, the high blood concentrations of M6G that occur with chronic morphine administration may mean that M6G contributes significant analgesic activity in patients receiving morphine for long periods of time.

Both M6G and M3G are larger molecules than morphine and therefore do not cross the blood-brain barrier as well as morphine. Certainly some of these metabolites should reach the brain where they could conceivably have an effect, but the significance of their role remains controversial. It has been suggested that both the analgesic response to morphine and the adverse effects experienced might depend on their M3G:M6G ratio. However, M3G:M6G ratios in morphine-resistant patients have been found to be similar to those in patients with well-controlled pain. Similarly, it has never been shown that metabolites influence the severity of side effects.

Laboratory evidence suggests some relation between specific metabolites and adverse side effects of morphine, which are listed in Table 8-1.

Table 8-1

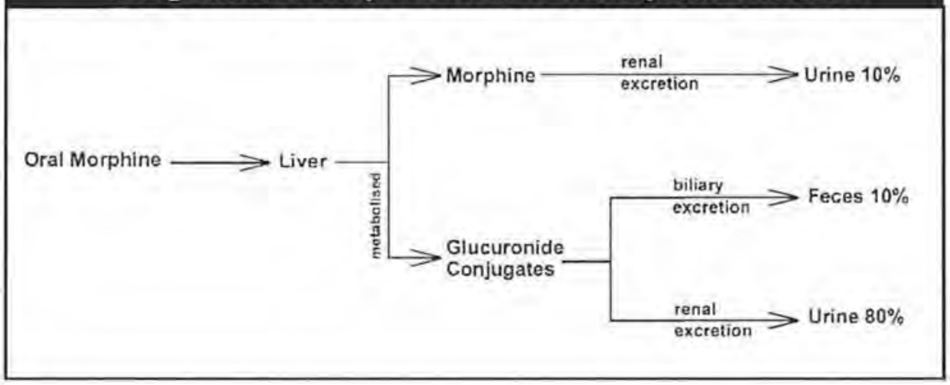
Morphine Metabolite Adverse Effects	
M6G (opioid receptor action)	M3G (nonopioid receptor action)
Drowsiness	Agitation
Nausea and vomiting	Myoclonus – seizures
Coma	Hyperalgesia
Respiratory depression	Delirium

Excretion

Elimination of the M3G and M6G metabolites by the kidneys accounts for 70% of the morphine that is eliminated from the body. Direct morphine (unchanged morphine) elimination in the urine (3%-10%), excretion of conjugates into the bile (7% to 10%) which is eliminated in the feces, and excretion via other routes (including conjugation to morphine-3-etheral sulfate and other forms) account for the remaining 30% of the morphine elimination. (See Figure 8-4).

Figure 8-4.

Diagrammatic Representation of Morphine Excretion



Effects of Hepatic and Renal Disease

Hepatic and renal disease can alter the bioavailability of a drug. In view of its extensive hepatic (liver) metabolism, the effects of morphine may be increased in patients with liver disease because the drug is not changed to forms that can

be easily eliminated. This is particularly significant in patients with advanced liver disease.

Renal impairment slows the clearance of morphine conjugates, resulting in accumulation of the active metabolite M6G (morphine6-glucuronide). Even modest levels of renal insufficiency can lead to a marked elevation of the morphine metabolites. Although most metabolites of morphine are inactive, the elevated metabolite levels may become significant in patients with renal failure resulting in a prolonged duration of action even with a single morphine dose. For these reasons, dosage reduction may be advisable in the presence of clinically significant renal impairment.

Elimination Half-Life

Morphine is rapidly eliminated from the body (the $t_{1/2}$ of morphine is 2-4 hours). Thus, oral morphine sulfate solution, which is rapidly absorbed, needs to be administered every few hours to maintain a prolonged, continuous analgesic effect. The advantage of KADIAN® in this respect is that it releases morphine for absorption over several hours, resulting in plasma morphine concentrations that are maintained for up to a 24-hour period, despite the short half-life of morphine.

Plasma Clearance

The plasma clearance of morphine (i.e., the volume of plasma cleared of the drug per unit time) after intravenous administration is 2.0 L/minute in healthy subjects and 1.2 L/minute in patients with cancer. These values, which are high, reflect the rapidity with which the body can eliminate morphine. Approximately 90% of an oral dose of morphine is excreted in the first 24 hours.

Pharmacodynamics of Morphine

The pharmacodynamics of a drug describe the relationship between the concentrations of the drug at the site(s) of action related to the magnitude of the effect(s) produced. In other words, pharmacodynamics explore what a drug does to the body.

The effects described below are common to all morphine-containing products.

Central Nervous System

The principal therapeutic actions of morphine are analgesia and sedation. The precise mechanism of analgesia is not know, however, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of the analgesic effects.

Respiratory Depression

Morphine produces respiratory depression (reduced breathing) by direction action on the respiratory centers in the brain stem. Morphine causes a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide levels in the blood. Morphine also reduces the responsiveness to electrical stimulation.

Cough Reflex

Morphine depresses the cough reflex through a direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Miosis

Morphine causes miosis (constriction of the pupils), even in total darkness. Pinpoint pupils are a sign of opioid overdose but can represent other disease processes as well (e.g. a stroke or bleeding in the pontine area of the brain).

Mydriasis

Marked mydriasis (dilation of the pupils) develops if severe hypoxia is present (as might occur with respiratory depression after an overdose).

Gastrointestinal Tract and other Smooth Muscle

Gastric, biliary, and pancreatic secretions are decreased by morphine.
Morphine causes a reduction in gastrointestinal motility due to an increase in tone in the antrum of the stomach (the muscular opening between the stomach and the duodenum). Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation.

Biliary spasm

Morphine can cause a marked increase in biliary tree pressure as a result of spasm of the sphincter of Oddi (the junction between the bile duct and the small intestine). Bile cannot pass through the sphincter into the small intestine, causing the increased pressure. This can result in severe abdominal pain.

Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension (decreased blood pressure when standing). Vasodilation can also contribute to symptoms of itching, flushing, eye redness, and sweating.

Histamine Release

Morphine can also cause a release of histamine into the system, which in turn can contribute to hypotension. Histamine release can manifest with itching, skin redness, eye redness, and sweating.

Plasma Level-Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentration-efficacy relationships have been demonstrated and suggest that opiate receptors occupy effector compartments, leading to a lag-time, or hysteresis, between rapid changes in plasma morphine concentrations and the effects of such changes.

The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady-state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately
5 to 20 ng/mL.

While plasma morphine-efficacy relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals. Dosages of morphine should be chosen and must be titrated on the basis of clinical evaluation of the patient and the balance between therapeutic and adverse effects.

Pharmacokinetics Summary of Immediate-Release Morphine

- Rapid and virtually complete oral absorption
- Undergoes extensive first-pass hepatic metabolism
- Low systemic bioavailability after oral dose due to first-pass hepatic metabolism (20%-40%)
- Short elimination half-life (2-4 hours)
- Extensive tissue distribution
- Relatively low plasma protein binding
- High plasma clearance
- Rapid elimination
- One or more pharmacologically active metabolites
- Excreted predominantly in the urine
- Pharmacokinetics are altered in hepatic and renal disease

Pharmacodynamics Summary of Morphine

- Therapeutic effects include analgesia and sedation

- Can cause respiratory depression by direction action on the respiratory centers
- Depresses the cough reflex
- Causes miosis (constriction of the pupils), even in total darkness
- Mydriasis (dilation of the pupils) develops if severe hypoxia is present
- Gastric, biliary, and pancreatic secretions are decreased by morphine
- Morphine causes a reduction in gastrointestinal motility due to an increase in tone—this leads to constipation
- Causes a marked increase in biliary tree pressure, which can lead to biliary spasm.
- Causes peripheral vasodilation which may result in orthostatic hypotension
- Causes a release of histamine into the system, which in turn can contribute to hypotension and can cause itching, skin redness, eye redness, and sweating.
- The analgesic effects and plasma morphine concentrations are related to the morphine dose.
- The minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 5 to 20 ng/mL.
- The effective dose in opioid-tolerant patients may be 10 to 50 times as great (or greater) than the appropriate dose for opioid-naïve individuals.

Pharmacokinetics of KADIAN®

Pharmacokinetic studies are divided into 2 general types: single dose or multiple dose. Single-dose studies typically involve healthy patients given one dose of the study medication. Multiple-dose studies may include healthy patients but are more likely to include patients using the medication for its intended purpose. Typically, the patients in multiple-dose studies have reached steady state equilibrium.

Single-Dose Pharmacokinetics

Absorption/Bioavailability

Morphine sulfate solution is used in clinical trials to represent immediate-release morphine. The area under the curve (AUC) is comparable for both KADIAN® and morphine sulfate solution, indicating that similar amounts of drug are absorbed from either preparation, so the total amount of absorbed drug is the same. However, the C_{max} (the peak serum concentration) produced by KADIAN® is lower than that

produced by morphine sulfate solution, which reflects the slower release of the drug.

The time to reach maximum concentration (t_{max}) is 8.5 hours with KADIAN® compared with 1.0 hours for morphine sulfate. KADIAN® maintains steady-state plasma morphine concentrations over 12 and 24 hours. The mean pharmacokinetic parameters of KADIAN® are provided in Table 8-2.

Table 8-2.

Mean Pharmacologic Parameters for Morphine after KADIAN® 50 mg and Morphine Sulfate Solution 25 mg (AUC and C_{max} results corrected to 50-mg dose)

Parameter	KADIAN® 50 mg	Morphine Sulfate Solution
AUC_{0-48} h (ng/mL)/h	120.2 (86.3 – 167.3)	112.8 (81.1 – 157.3)
$AUC_{0-\infty}$ (ng/mL)/h	153.3 (107.2 – 219.5)	190.0 (149.5 – 241.4)
C_{max} (ng/mL)	7.3* (4.6 – 11.6)	29.6 (20.5-43.0)
t_{max} (h)	8.5 + 4.5*	1.0 + 0.3
$t > 0.75\ C_{max}$ (h)	6.7 + 6.8*	0.9 + 0.4
$t_{1/2\alpha}$ (h)	18.3 + 8.3*	24.4 +10.9
$t_{1/2\beta}$ (h)	ND	2.2 + 0.4

AUC = area under the plasma concentration curve.
C_{max} = maximum plasma drug concentration
t_{max} = time to reach maximum plasma concentration
$t > 0.75\ C_{max}$ (h) = time until plasma concentration is ≥ 75% of C_{max} (a comparative measure for extended-release formulations.)
ND = not determined
$t_{1/2\alpha}$ = half-life for the first phase of elimination
$t_{1/2\beta}$ = terminal half-life
Table is adapted from Maccarrone et al. Drug Invest 1994;7(5):262-274

Dose Proportionality

Most drugs have a proportionate relation between drug concentration in the serum and dosing. That is, the amount of drug given relates directly to the serum concentrations. In pharmacokinetic terms, this is called a linear pharmacokinetic profile. This means that serum drug concentrations change proportionally (arithmetically) with daily dosing, given time to come to steady state concentrations. For example, in a drug with

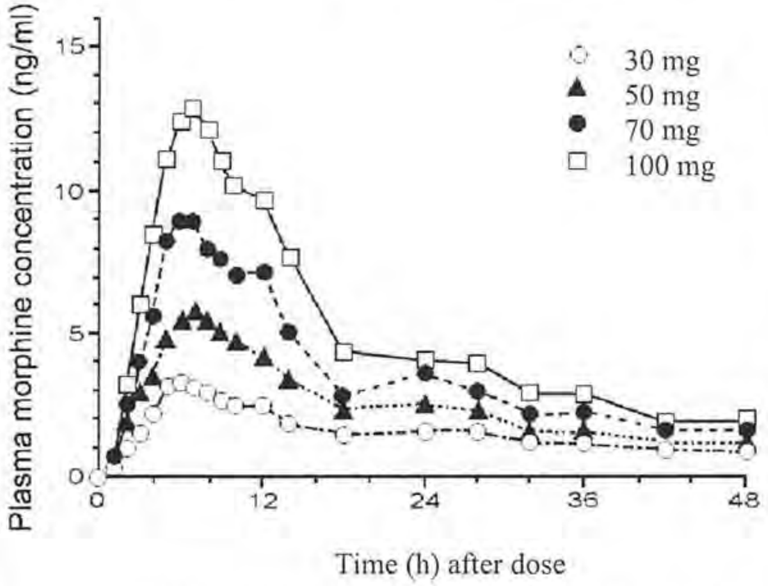
linear absorption and excretion pharmacokinetic properties, the serum concentration would double when the dose amount doubled. Nonlinear pharmacokinetic properties make it more complex to determine how the serum concentrations would change for a given change in dose. An example of nonlinear pharmacokinetics would be a drug that requires metabolism in the liver to become active, but at very high doses the liver enzyme system is saturated and can no longer increase its speed of metabolism despite increasing doses. In this case, the drug concentrations would begin to very rapidly rise when the liver enzyme system is saturated, leading to a loss of the proportional relation between the dose and the serum concentrations.

The dose of morphine often requires upward or downward adjustment during the course of therapy. Therefore, it is important that different strengths of the same formulation be dose-proportional to facilitate a safe and predictable transfer from one strength to another. The plasma morphine concentration for 4 single doses of KADIAN® (30, 50, 70, and 100mg) administered to 24 healthy volunteers in a crossover study design are shown in Figure 8-5. Both the C_{max} and the AUC increased in direct proportion to the increment in the KADIAN® dose. Thus, KADIAN® exhibited linear pharmacokinetics over the dose range tested. The t_{max} and terminal half-life did not differ across doses.

This means that if you know roughly what change in serum concentrations to expect from a 10-mg dose increase, the change will be consistent whether the 10-mg change is from 20 mg to 30 mg or from 50 mg to 60 mg. Drugs that have a linear (proportionate) relation between absorption and serum concentrations are preferable because it is easier to estimate dosage changes.

Figure 8-5

Mean Plasma Morphine Concentration-Time Profiles for KADIAN® 30, 50, 70, and 100mg



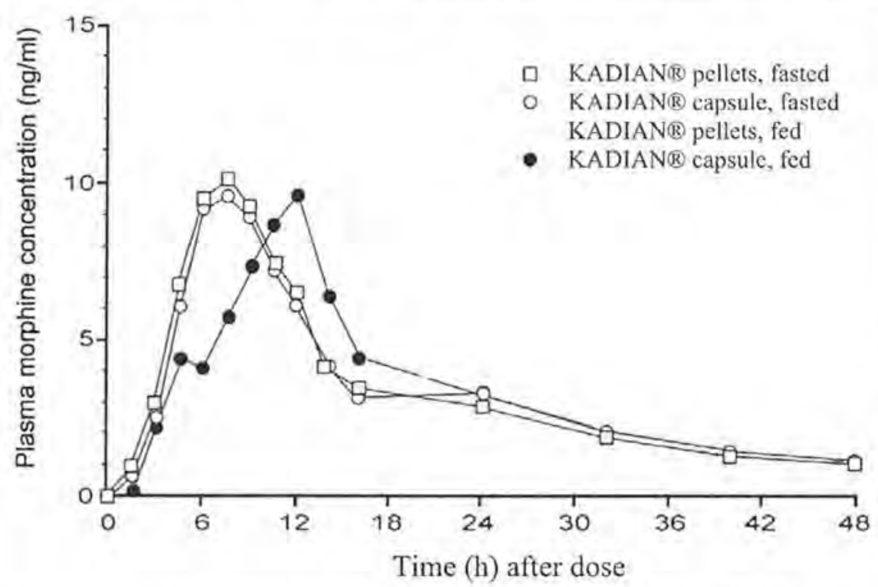
Adapted from Maccarrone C, et al. Drug Invest 1994;7(5):262-274.

Food Effects

Consistent absorption of the active ingredient when taken with or without food is a desirable feature for any drug formulation. The extent or AUC of morphine absorption from KADIAN® capsules is not significantly affected by the presence of food. C_{max} is slightly less after a meal, but this is not considered to be significant. Food does slow the rate of absorption; t_{max} is lengthened to 10.1 hours. Thus, KADIAN® can be taken with or without food.

Figure 8-6

Mean Plasma Morphine Concentration-Time Profiles for KADIAN® 50-mg Capsules (fed and fasted) and KADIAN® Pellets (fed and fasted)



Adapted from Broomhead A, et al. *Clin Drug Invest* 1997;14(2):137-145.

Administration by Sprinkling

Another benefit of KADIAN® is that the rate of release of morphine from the pellets has not been shown to be affected when the pellets are poured onto applesauce before ingestion.

Figure 8-6 and Table 8-3 present data from a clinical study aimed at evaluating the pharmacokinetic profile and relative bioavailability of KADIAN® administered as a whole capsule or as an equivalent dose of pellets sprinkled onto a small amount of applesauce. In this study, 25 healthy male and female volunteers each received single 50-mg doses of KADIAN® capsules or pellets under both fed and fasted conditions, in a 4-period crossover study design.

Table 8-3

Mean Pharmacokinetic Parameters for Morphine after KADIAN® 50-mg Capsules (fed and fasted) and KADIAN® 50-mg Pellets

Parameter	KADIAN® Capsules Fasted	KADIAN® Pellets Fasted	KADIAN® Capsules Fed	KADIAN® Pellets Fed (in applesauce)
AUC_{0-48h} (ng/ml)/hr[a]	154.5 (110.9-212.8)	154.8 (110.1-213.9)	153.3 (1 08.6-212.2)	149.0 (1 06.2-204.3)
$AUC_{0-\infty}$ (ng/ml)/h[a]	182.4 (132.4-248.6)	178.5 (125.9-248.4)	175.7 (126.0-214.8)	172.1 (125.6-232.5)
Cmax (ng/ml)[a]	10.0 (6.8-4.7)	10.5 (5.7-1.77)	9.7 (6.3-14.6)	8.3[c*] (5.3-12.7)
tmax (h)[b]	7.4+1.5[d*]7.9	+2.0[d*]11.6	+1.4	11.6 + 3.8
t1/2 á (h)[b]	17.0 + 5.0	16.3 + 4.4	15.1 + 3.2[f*]	15.0 + 2.9f*

a Geometric Means + 1 SD range in parentheses
b Arithmetic means + l SD.
c Significantly less than KADIAN® pellets fasted and KADIAN® capsule fed.
d Significantly less than KADIAN® pellets fed.
e Significantly less than KADIAN® pellets fasted.
** Statistically significant difference between treatments (p< 0.05 by ANOVA and t-test)*
Abbreviations: AUC = area under the plasma concentration time curve; C max = maximum plasma drug concentration; t max = time to reach Cmax; t1/2 = terminal half-life.
Adapted from Broomhead A, et al. Clin Drug Invest 1997;14(2)137-145.

As previously described in the section on food effects, there was a slight decrease in C_{max} and a delay in t_{max} for KADIAN® administered under fed conditions as compared with administration under fasted conditions. Importantly, the data also show that for similar conditions of food intake (fasted or fed conditions) there were no significant differences in pharmacokinetic parameters between KADIAN® capsules swallowed whole and KADIAN® pellets sprinkled on applesauce. Thus, under fasted conditions, KADIAN® capsules and KADIAN® pellets were bioequivalent and under fed conditions, KADIAN® capsules and KADIAN® pellets were bioequivalent.

Sprinkling of KADIAN® pellets onto a small amount of applesauce offers an attractive mode of administration for patients who have difficulty swallowing capsules or tablets as a result of disease progression, general debility, or the effects of radiation and chemotherapy.

The extent of absorption of morphine from KADIAN® capsules is similar to controlled-release morphine tablets and morphine sulfate solution. Gourlay (1998) reviewed the single-dose and multiple-dose pharmacokinetics of KADIAN® and other extended-release morphine formulations. Steady state pharmacokinetics and comparisons with other controlled-release products are discussed in Chapter 11.

Pharmacokinetics Summary of KADIAN®

- The AUC is comparable for both KADIAN® and morphine sulfate solution, indicating that similar amounts of drug are absorbed from either preparation.
- The C_{max} (the peak serum level) produced by KADIAN® is lower than that produced by morphine sulfate solution, reflecting the slower release of the drug. This is a characteristic of an extended release formulation and may result in fewer side effects.
- The slow rate of drug release in the gastrointestinal tract leads to a slow rate of absorption.
- The rate of absorption is slowed marginally by food but this is not clinically relevant, because bioavailability is not significantly affected.
- KADIAN® provides adequate plasma morphine concentrations, which permits once daily dosing.
- The dose-serum concentration relationship is linear, making it easier to predict changes in serum concentrations when doses are changed.
- KADIAN® absorption is the same whether the dose is taken as a whole capsule or sprinkled on applesauce.
- The unique pharmacokinetic profile of KADIAN® indicates that it has extended-release properties that provide the option of 24-hour pain control with a single daily dose. However, a patient's response to morphine is highly individualized and there is no demonstrated correlation between blood plasma concentrations and the degree of pain relief that each patient will experience.

Summary

- Morphine is extensively distributed throughout the body, and does not accumulate in tissues when given in normal doses. Only a relatively low proportion (30%-35%) of morphine present in the bloodstream is bound to plasma proteins. Thus, alterations in the degree of protein binding of morphine would not be expected to

influence plasma concentrations of free (pharmacologically active) morphine to any appreciable extent.

- Morphine is rapidly eliminated from the body and has a short plasma elimination half-life (2 to 4 hours). Thus, oral morphine sulfate solution, which is rapidly absorbed, needs to be administered every 4 hours in an attempt to maintain continuous analgesia. The extended-release formulation of KADIAN® is advantageous in that it allows plasma morphine concentrations to be maintained for up to a 24-hour dosing intervals.
- The major metabolic pathway of morphine involves glucuronidation, which occurs predominantly in the liver. Thus, the effects of morphine may be increased in patients with hepatic disease. Because morphine is excreted primarily via the kidneys, renal impairment slows the clearance of morphine conjugates, resulting in accumulation of the active metabolite morphine-6-glucuronide (M6G). For this reason, dosage reduction may be advisable in the presence of clinically significant hepatic or renal impairment.
- KADIAN® consists of polymer-coated pellets of morphine. The less acidic environment of the small intestine leads to gradual pH-dependent release of morphine from the pellets over several hours, maintaining plasma morphine concentrations for up to a 24-hour period. Thus, although the extent of absorption of morphine from KADIAN® capsules is similar to that of morphine sulfate solution or controlled-release morphine tablets, the rate of absorption of morphine from KADIAN® capsules is significantly slower.

Literature Cited

Maccarrone et al. Drug Invest 1994;7(5):262-274

Broomhead A, et al. Clin Drug Invest 1997;14(2):137-145.

Self-Assessment Test

Circle the best response

1). An extended-release formulation of a drug allows the - ______________________________.
   a. dosing interval to be extended
   b. Half-life to increase
   c. AUC to decrease
   d. Absorption rate to increase

2). The lower bioavailability of orally administered morphine compared with parenterally administered morphine is largely accounted for by a ________________________.
   a. Slower rate of absorption of oral morphine.
   b. Lower C_{max} obtained with oral morphine
   c. Extensive first-pass metabolism of oral morphine
   d. High rate of clearance of oral morphine

3). The time to peak plasma morphine concentrations after administration of oral morphine sulfate solution is approximately __________hours.
   a. 1 c. 3
   b. 2 d. 4

4). The time to peak plasma concentrations after KADIAN® administration is approximately _________hours.
   a. 2 c. 6
   b. 4 d. 8

5). Glucuronidation, the major metabolic pathway of morphine, occurs primarily in the ________________.
   a. Kidneys c. Brain
   b. Liver d. Tissues

6). Which statement is true regarding the protein binding of morphine sulfate?
   a. Morphine is highly protein bound.
   b. The plasma concentration of morphine is not appreciably affected by alterations in plasma protein binding.
   c. Only morphine sulfate bound to proteins is pharmacologically active.
   d. Other drugs that are highly protein bound would influence drug concentrations or morphine sulfate if given concomitantly.

7). Which statement is true regarding the morphine metabolites M6G and M3G?
   a. M3G is pharmacologically inactive.
   b. More M6G is produced than M3G.
   c. The pharmacologic effects of morphine are due primarily to M6G.
   d. More M6G is produced after administration of KADIAN® than after immediate-release morphine administration.

8). The rapid elimination of morphine from the body is reflected by its___________________.
   a. Long half-life.
   b. High rate of plasma clearance.
   c. Slow rate of absorption.
   d. Significant metabolite production.

True or False

9). Pharmacokinetics is the study of the absorption, distribution, metabolism, and excretion of pharmaceutical agents.
   a. True
   b. False

10). The extent of morphine absorption from KADIAN® capsules is decreased by the presence of food.
   a. True
   b. False

11). The oral bioavailability of morphine normally ranges from 10% to 20%.
   a. True
   b. False

12). KADIAN® shows nonlinear pharmacokinetics over a dose range of 30 to 100 mg.
   a. True
   b. False

13). Steady state plasma morphine concentrations are achieved within 12 to 24 hours of starting KADIAN® therapy.
   a. True
   b. False

14). The kidneys are the primary route of excretion of morphine.
   a. True
   b. False

Answers to Self-Assessment Test

1. a	8. b
2. c	9. a
3. a	10. b
4. d	11. b
5. b	12. b
6. b	13. b
7. c	14. a

CHAPTER NINE

Dosage and Administration

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Describe the factors to be considered in selecting the initial dose of KADIAN®.
- Describe the key factors in switching a patient from another opioid to KADIAN®.
- Describe the potential adverse interactions of KADIAN® with other medications.
- Describe the key information to be provided to patients taking KADIAN®.

Terminology

Bioequivalent drugs:	Two drugs that are similar in absorption and physiologic activity.
Breakthrough pain:	Pain that is not fully controlled with the current pain control regimen. It may be episodic.
Dosing interval:	The time between administration of doses.
Dose titration:	Adjustment of a dose to achieve the best therapeutic response with a minimum of undesirable side effects.
Equianalgesic dosing:	A dose of an analgesic drug that is equivalent in strength to a dose of another analgesic drug.
Extent of absorption:	The degree to which a dose of medication is taken up into the system from the site of administration.
French:	A measurement scale used for denoting the external diameter of catheters, sounds, and other tubular instruments. The scale is expressed in units, and each unit equals about 0.33mm. Thus, a 16-French catheter has a 5.3-mm external diameter (16 X 0.33mm).
Gastrostomy:	The creation of an opening in the stomach through which a tube is placed to allow administration of fluids, food, and medications in individuals who cannot swallow.
Gastrostomy tube:	A tube inserted through a gastrostomy opening into the stomach of a patient used for feeding. It is also known as a "G-tube" or a "feeding tube." There is a small balloon on the tube that is inflated within the stomach to prevent the tube from falling out and a closed port on the end of the external section of the tube that can be opened to allow fluids and medications to be administered. Water and other fluids can be flushed through the tube from the opening of the port to clear obstruction or to make sure all the material introduced has fully passed through into the stomach. (Note: not a NG tube)
Incident or episodic pain:	Pain that occurs in addition to a patient's usual pain. An example would be chronic pain that is intensified by extra physical activity.
Nasogastric tube:	A tube of soft rubber or plastic that is inserted through a nostril into the stomach. This tube is used for various medication problems, including decompressing/draining the stomach of gas or digestive fluids if it becomes distended due to obstruction. Nasogastric tubes are of a relatively small diameter to maintain patient comfort, therefore are prone to blockage if material (e.g. medications or food) are administered through them. (Note: not a NG tube)
Parenteral:	Administration of a drug by means other than absorption through the intestine. These methods include intravenous, intramuscular, or subcutaneous delivery of a drug.
Trough:	The lowest level of drug concentration in the blood.

Introduction

KADIAN® is a extended-release formulation of morphine sulfate that is composed of polymer-coated pellets of drug presented in capsule form. Eight color-coded dose strengths are available: 10 mg (light blue), 20 mg (yellow), 30 mg (blue violet), 50 mg (blue), 60 mg (pink), 80 mg (light orange), 100 mg (green), and 200 mg (light brown). These permit flexible dose titration. This chapter will review recommendations for administration and dosing of KADIAN®.

Administration

KADIAN® has three modes of administration that permit dosing flexibility. KADIAN® can be given as a whole capsule, by sprinkling the contents of the capsule on applesauce , or through a gastrostomy tube, 16 French or larger.

The safety of KADIAN® has not been directly investigated in patients under the age of 18 years.

Whole Capsule Administration

KADIAN® capsules should be swallowed whole. The capsules or pellets should not be chewed, crushed, or dissolved, however, as this could lead to the rapid release and absorption of a potentially toxic dose of morphine.

Sprinkle Administration

In a study of healthy volunteers, KADIAN® pellets sprinkled over applesauce were found to be bioequivalent to KADIAN® capsules swallowed whole with applesauce under fasting conditions. [Add reference - Kerr and Tester] Other foods have been tested but are not approved by the FDA. Patients who have difficulty swallowing whole capsules or tablets may benefit from this alternative method of administration.

Directions for sprinkle administration

1. Open capsule.
2. Sprinkle the entire contents of the capsule (i.e., all pellets) into a small amount of applesauce. Applesauce should be room temperature or cooler.

3. Use immediately.
4. The contents of the capsule should not be chewed or crushed, because this increases the risk of a toxic or fatal overdose.
5. Rinse mouth to ensure that all pellets have been swallowed.
6. Patients should consume the entire portion and should not divide the applesauce into separate doses.

Gastrostomy Tube (G-tube) Administration:

The pellets in KADIAN® capsules are small enough to pass through a 16-French (or larger) gastrostomy tube and may be administered in this manner to patients with a gastrostomy tube in place. Follow these procedures and principles when using KADIAN® by G-tube administration:

1. Fit 16-French or larger G-tube with a funnel at the port end of the G-tube. Flush the G-tube with water to ensure that it is wet prior to administration.
2. Open capsule and sprinkle the entire contents (i.e., all pellets) into 10mL of water in a beaker or other appropriate container.
3. Use a swirling motion to pour the pellet-water mixture through the funnel and into the G-tube.
4. Rinse the beaker or container with an additional 10mL of water and pour this through the G-tube.
5. Repeat rinsing until no pellets remain in the beaker.

The administration of KADIAN® pellets through a nasogastric tube should not be attempted.

Dosage

The extended-release nature of KADIAN® allows it to be given on either a once-a-day (Q24h, every 24 hours) or twice-a-day (Q12h, every 12 hours) schedule. To avoid accumulation of morphine, the dosing interval of KADIAN® should not be more than every 12 hours. KADIAN® produces analgesia similar to that produced by immediate-release and controlled-release formulations for the same total daily dose of morphine.

Patients who do not have a proven tolerance to opioids should be treated to clinical response (i.e., the pain control goal for the patient has been reached) using an immediate-release morphine formulation and should then be converted to an extended-release product. However, if KADIAN® is chosen as the initial opioid, the patient should be started on the 20-mg strength dosage. The dose may be increased by 20 mg every other day. Dosage adjustment is needed until the patient has achieved the best balance between baseline analgesia and opioid side effects such as confusion, sedation, nausea and vomiting, and constipation.

In opioid-tolerant patients, KADIAN® should be started by administering one-half of the estimated total daily oral morphine dose every 12 hours or 24 hours. The dose should be titrated no more frequently than every other day to allow the patient to stabilize on the new dose before increasing the dose. **The 100-mg and 200-mg capsules are only for use in patients who are known to be opioid-tolerant.**

Considerations in the Adjustment of Dosing Regimens

Adjustments in the dosage regimen of KADIAN® can be made to minimize side effects in patients having trouble tolerating KADIAN® or other opioids. Adjustments can be done by decreasing the strength of the dose or decreasing the frequency of dosing.

- For example, if the patient is started on KADIAN® every 24 hours and excessive opioid side effects are observed, the next dose should be reduced in strength. If dose reduction leads to inadequate analgesia, consider keeping the dose at the lower total dose, but increasing the dosing interval to every 12 hours. This may permit adequate plasma drug levels to maintain pain control without the higher drug levels associated with side effects. Inadequate analgesia may include end of dose pain, breakthrough pain, incident pain, or simply inadequate baseline pain relief. If inadequate analgesia or pain occurs on a 12-hour dosing regimen, a supplemental dose of a short-acting analgesic may be given as an alternative to the higher doses of long-acting opioids. If breakthrough pain continues despite these attempts to minimize side effects, the dose of KADIAN® may be increased cautiously. About half of patients with cancer-related pain will require dose escalation. (Zech 1995) In a study of patients with non-cancer chronic pain, 44% required dose escalation by 3 months, 23% in the second three month follow up period, and then for 10% in each follow-up period thereafter. (Portenoy 2007)

Some patients experience the majority of side effects only at the time of peak plasma concentration. For these patients, an alternative is to give the dose in the late

afternoon. The peak plasma concentration will then occur during the sleep cycle when the patient will be less aware of side effects.

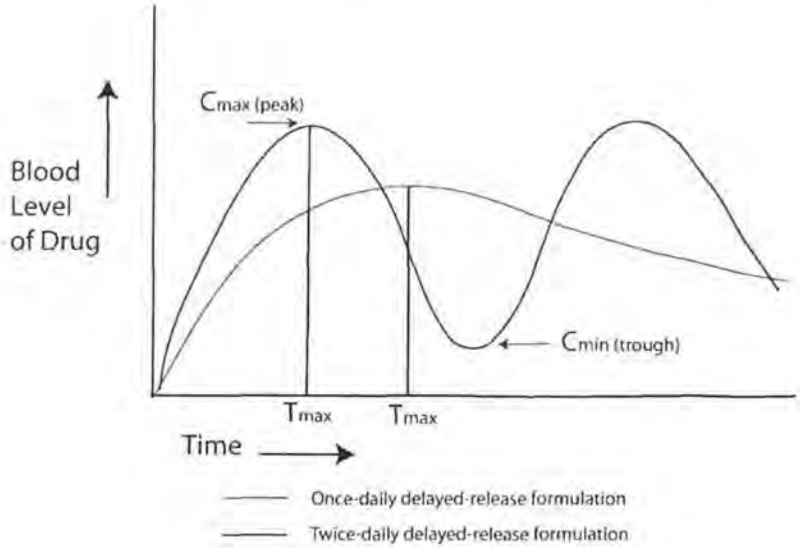
Bioequivalence

KADIAN® capsules have the same extent of absorption (also referred to as "area under the curve" or AUC; see Chapter 8 on pharmacokinetics for full description) as immediate-release and controlled-release oral formulations of morphine sulfate. This means that the total amount of morphine absorbed is the same for an equivalent morphine dose, whether given as an extended-release or immediate-release form.

> KADIAN® capsules have the same extent of absorption as immediate-release and controlled-release oral formulations of morphine sulfate. The total amount of morphine absorbed is the same, but the time to peak blood levels and the maximum concentrations in the blood are lower with the extended release formulation.

However, key pharmacokinetic parameters of immediate-release formulations and some extended-release formulations differ from those of KADIAN®. The time to peak blood levels (T_{max}) is prolonged and the maximum serum concentration level (C_{max}) is lower with KADIAN®. Thus, the immediate-release and some extended-release products are not bioequivalent to KADIAN®. Drug products are bioequivalent when the rates and extent of bioavailability of the active ingredient in the products are not significantly different under suitable test conditions.

Figure 9-1: Differences in Peak and Trough Concentrations and T_{max} between once-daily and twice-daily delayed-release preparations



Conversion from KADIAN® to the same total daily dose of other controlled-release morphine preparations may lead to either excessive sedation at peak serum concentrations or inadequate analgesia at trough serum concentrations. This is because the T_{max} may occur more rapidly and the C_{max} may be higher with the other preparation than with KADIAN®. These rapid and higher peak levels may be associated with increased side effects; therefore, close observation and appropriate dosage adjustments are recommended in this situation.

Selection of a KADIAN® Starting Dose

It is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior opioid analgesic treatment experience. In the selection of the initial dose of KADIAN®, attention should be given to

- the total daily dose, potency, and kind of opioid the patient has been taking previously;
- the reliability of the relative potency estimate used to calculate the equivalent dose of morphine needed;
- the patient's degree of opioid tolerance;
- the general condition and medical status of the patient;
- concurrent medication(s); and
- the type and severity of the patient's pain.

Conversion from other oral morphine to KADIAN®

Patients taking other oral morphine formulations may be converted to KADIAN® by totaling the daily dose of morphine and giving one-half of the total as daily dose KADIAN® capsules every 12 hours. The first dose of KADIAN® may be given with the last dose of conventional oral morphine because of the long delay until the peak effect after administration of KADIAN®. For example, if a patient had been previously taking a total of 60 mg of immediate-release morphine each day, the initial starting dose of KADIAN® could be 30 mg twice daily.

Equianalgesic Tables

Patients who have never been treated with opioids should be started on the low, recommended starting doses because these patients lack tolerance to opioids. However, patients who are already receiving opioids are likely to have developed tolerance and may experience insufficient pain relief and possibly withdrawal if adequate doses are not administered. Because opioids have different formulations and potencies, it is important to know what strengths of a new opioid drug are equal to the strength of the formulation that the patient is currently being treated with. For example, if a patient is taking 200mg of codeine a day, they might be started at the equivalent dose of morphine, 60mg, given as 30mg twice daily.

Multiple tables of oral and parenteral opioid equivalents are available for use to guide these conversions. These tables are called equianalgesic-dosing tables. Although the equianalgesic doses are equal in theory, in practice, there is variable cross-tolerance to opioids among individual patients. In addition, the ratios obtained from these tables are only approximate; therefore use caution when converting a patient from one opioid or one dosage form to another. It may be advisable to initiate the dose of the converted opioid at 50% of the first opioid to avoid excessive side effects unless a patient is in severe pain.

There are several methods to help you convert from one opioid drug or dosage form to another. Because there are several ways to calculate an equianalgesic dose, the choice of method is primarily one of individual preference.

Ratios

Using the equianalgesic chart in Table 9-1 as an example, note that the chart provides a list of analgesics at doses, both oral and parenteral, that are approximately equal to each other in the ability to provide pain relief. In other words, all the doses are theoretically interchangeable. All the opioid doses listed in the equianalgesic chart are appropriate starting doses given every 4 hours for adults with severe pain.

Example: Oral Morphine to IV Morphine

- Look at Table 9-1 and find the oral dose listed for morphine (30 mg) and the parenteral dose (10 mg).
- This gives a 30:10 or a 3:1 ratio for oral to parenteral morphine.
- This means that it takes approximately 3 times more morphine orally than parenterally (e.g., IV) to produce the same analgesic effect.
- One can simply divide any oral morphine dose by 3 to determine the approximate equianalgesic parenteral morphine dose.
- For safety reasons, this dose is often halved for initial dosing, because it may be difficult to predict side effects. The dose is increased if the patient tolerated the initial dose and needs additional pain relief.

Table 9-1

Equianalgesic Table Adapted from Goodman and Gilman, 9th Edition		
Drug	Parenteral (mg)	Oral (mg)
Morphine	10	30 – 60**
Hydromorphone	1.3	7.5
Oxymorphone	1	5 (rectal)
Oxycodone	-	5-10*
Codeine	130	200
Hydrocodone	-	5-10*
Propoxyphene	-	65*
Meperidine	75	300
Levorphanol	2	4
Methadone	10	20
Fentanyl	0.1 µg	-
Nalbuphine	10	-
Butorphanol	2	-

*The dose of propoxyphene is not necessarily equivalent to 10 mg of subcutaneous morphine.

Example: Conversion from IV morphine to KADIAN®

- When converting IV morphine to oral morphine, use the same equianalgesic dose described above. In this instance, the ratio is 1:3.
- Simply multiply any IV morphine dose by 3 to determine the approximate equianalgesic oral morphine dose.
- If you want to take 20 mg IV total daily dose of morphine and convert it to KADIAN®, you would multiply 20 mg IV morphine by 3 to get 60 mg oral KADIAN® (60 mg once a day OR 30 mg twice a day).
- For safety reasons, KADIAN® may be started at a lower dose.

Proportions

Another method of calculating equianalgesic doses (EAD) is to set up simple math proportions using ratios. Use the following equation to calculate equianalgesic doses. Do a separate calculation for each old drug and route.

$$X = \text{Old dose} \times \frac{\text{New drug EAD}}{\text{Old drug EAD}}$$

Where X = Total daily dose of new drug

New drug EAD = Equianalgesic dose from chart of new drug and route

Old dose = Total daily dose of old drug

Old drug EAD = Equianalgesic dose from chart of old drug and route

Example: Conversion of KADIAN® to IV morphine

- Use the proportion equation to estimate the required parenteral morphine dose for a patient taking 60 mg of KADIAN®.
- In this example, the "new drug" will be IV morphine and the "old drug" is KADIAN®.
- Look at Table 9-2 to find equianalgesic doses for morphine IV ("New drug EAD") and oral morphine ("Old dose").

$$X = 60\text{ mg} \times \frac{10\text{ mg}}{30\text{ mg}} = 20\text{ mg}$$

- After you insert the numbers into the equation, you find that $X = 20$ mg IV morphine daily.
- Consider decreasing the total daily dose by 50% for safety (10 mg).
- The dose is then divided by the number of times a day the dose will be given. The dose interval is based on duration of action of the drug.
- IV morphine is given approximately every 4 hours, so 3 mg of IV morphine given every 4 hours would give the total of 10 mg (50% of the total calculated equivalent dose) given over 24 hours.

- This approach is likely to require a dosage increase in the first 24 hours for many patients (because it was started at 50% of the equivalent dose of the old drug), but is recommended because it is less likely to cause overdose or undesirable side effects than going directly to the calculated equivalent dose without titration.

Use of KADIAN® as the First Opioid Analgesic

There has been no evaluation of KADIAN® as an initial opioid analgesic in the management of pain. Because it may be more difficult to titrate the doses to achieve adequate analgesia when using extended-release morphine, it is ordinarily advisable to begin treatment with an immediate-release morphine formulation.

Opioid analgesic agents may not effectively relieve all types of pain. For example, neuropathic pain and headaches often require treatment with other types of medications containing analgesic properties. This does not mean that patients suffering from these types of pain should not be given an adequate trial of opioid analgesics. However, such patients may need to be promptly evaluated for other types of pain therapy.

Table 9-2

Equianalgesic Table Adapted from APS		
Drug	Parenteral (mg)	PO (mg)
Morphine	10	30

Hydromorphone	1.5	7.5
Oxymorphone	1	10 (rectal)
Oxycodone	-	20
Meperidine	75	300
Levorphanol	2(acute) 1 (chronic)	4(acute) 1 (chronic)
Methadone	10(acute) 2-4 (chronic)	20(acute) 2-4 (chronic)
Fentanyl	0.1	-

Individualization of Dosage

The use of opioid analgesics in the management of chronic malignant and chronic benign pain is described in materials published by the World Health Organization (WHO), the Agency for Health Care Research and Quality, and the American Pain Society, which are available from Alpharma Pharmaceuticals LLC upon request. Treatment should be individualized by using appropriate pain management principals.

KADIAN® is a third-step drug that is most useful when the patient requires a constant level of opioid analgesia as a "foundation" or "baseline." When a patient has reached the point where comfort cannot be provided with a combination of nonopioid medications (NSAIDs and acetaminophen) and intermittent use of moderate or strong opioids, the patient's total opioid therapy should be converted into a 24-hour oral opioid equivalent. The addition of KADIAN® is done to provide a constant level of analgesia, and the level of analgesia can then be supplemented by the use of other medications (e.g., NSAIDs) as needed.

If breakthrough or incident pain occurs, the dose may be supplemented with a small dose (less than 20% of the total daily dose) of an immediate-release opioid analgesic. Patients who are excessively sedated after a once-a-day dose or who regularly experience inadequate analgesia before the next dose should be switched to Q 12 hr. dosing. If two or more breakthrough medications are needed, titration of the baseline or long-acting opioid medication should be done.

Pure mu-agonist opioids do not have a maximum dose. Doses are titrated to pain relief, and so no ceiling can be

> Pure mu-agonist opioids do not have a maximum dose; doses are titrated to pain relief.

given as to the recommended maximal dose. The total dose of KADIAN® should be advanced until the desired therapeutic endpoint is reached or clinically significant opioid-related adverse reactions occur.

Information for Patients

Patients receiving KADIAN® should be given the following instructions by the medical practitioner:

1. Patients should be advised that KADIAN® contains morphine and should be taken only as directed.
2. Patients should be advised that KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternately, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of apple sauce immediately prior to ingestion. KADIAN® capsules or the contents of the capsules must not be chewed or crushed due to a risk of fatal overdose.
3. Patients should be advised that KADIAN® 100 mg and 200 mg Capsules are for use only in opioid-tolerant patients. Special care must be taken to avoid accidental ingestion or use by individuals (including children) other than the patient for whom it was originally prescribed, as such unsupervised use may have severe, even fatal, consequences.
4. Patients should be advised that the dose of KADIAN® should not be adjusted without consulting the prescribing health care provider.
5. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
6. Patients should be advised that KADIAN® may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients started on KADIAN® or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
7. Patients should be advised that KADIAN® should not be taken with alcohol or other CNS depressants (sleeping medication, tranquilizers) except by the orders of the prescribing healthcare provider because dangerous additive effects may occur resulting in serious injury or death.

8. Women of childbearing potential who become or are planning to become pregnant, should consult their prescribing healthcare provider prior to initiating or continuing therapy with KADIAN®.
9. Patients should be advised that if they have been receiving treatment with KADIAN® for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the KADIAN® dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their prescribing healthcare provider should provide a dose schedule to accomplish a gradual discontinuation of the medication.
10. Patients should be advised that KADIAN® is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
11. Patients should be advised that severe constipation could occur as a result of taking KADIAN® and appropriate laxatives, stool softeners and other appropriate treatments should be initiated from the beginning of opioid therapy.
12. Patients should be instructed to keep KADIAN® in a secure place out of the reach of children. When KADIAN® is no longer needed, the unused capsules should be destroyed by flushing down the toilet.

FDA Safety Warnings for KADIAN®

The following are included in black box warnings from the FDA regarding KADIAN®:

- KADIAN® contains morphine sulfate, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. KADIAN® can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing KADIAN® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.
- KADIAN® capsules are an extended-release oral formulation of morphine sulfate indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.
- KADIAN® capsules are **NOT** for use as a **PRN** analgesic.
- KADIAN® 100-mg and 200-mg capsules ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. Ingestion of these capsules or of the pellets within the capsules may cause fatal respiratory depression when administered to patients not already

tolerant to high doses of opioids. KADIAN®.capsules are to be swallowed whole or the contents of the capsules sprinkled on applesauce. The pellets in the capsules are not to be chewed, crushed, or dissolved due to the risk of rapid release and the absorption of a potentially fatal dose of morphine.

Additional warnings included in the prescribing information are as follows:

- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.

Summary

- KADIAN® is available in color-coded 10 mg (light blue) 20-mg (yellow), 30-mg (blue violet), 50-mg (blue), 60-mg (pink), 80-mg (light orange), 100-mg (green), and 200-mg (brown) capsules. KADIAN® capsules are administered orally once or twice daily (Q12 or Q24 hours). KADIAN® capsules should be swallowed whole (not chewed, crushed, or dissolved). Alternatively, KADIAN® capsules may be opened and the entire contents sprinkled on a small amount of applesauce immediately before ingestion, or the pellets can be mixed with a small amount of water and administered through a 16-French (or larger) gastrostomy tube. The administration of KADIAN® pellets through a nasogastric tube should not be attempted.
- KADIAN® may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression because respiratory depression, hypotension, and profound sedation or coma may result.
- The pellets in KADIAN® should not be chewed, crushed, or dissolved because of a risk of overdose.
- Selection of the initial KADIAN® dosage should take into account the total daily dose, potency and characteristics of previously administered opioid analgesics, the reliability of the relative potency estimate used to calculate the total dose of morphine required, the patient's degree of opioid tolerance, the patient's general medical condition, other medications that the patient is concurrently taking, and the type and severity of the patient's pain.
- Patients already taking other oral morphine formulations can be converted to KADIAN® therapy by administering the patient's current total daily morphine dose of KADIAN® every 24 hours or one-half of the patient's current total daily morphine dose of KADIAN® every 12 hours, with subsequent dosage

adjustments as necessary.

- Patients already taking parenteral morphine or other parenteral or oral opioids should be converted with caution to KADIAN® because of individual patient variations and uncertainties regarding relative estimates of opioid potency and cross-tolerance. Only approximate guides as to the relative potencies of opioids are available. Researchers suggest that, for morphine, an oral dose 3 times greater than the parenterally administered dose is equipotent, but specific recommendations cannot be made for conversion from other parenteral or oral opioids to oral morphine. In these circumstances, the initial KADIAN® dosage regimen chosen should be conservative and 24-hour morphine requirements should, if anything, err on the side of underestimation.

Literature Cited

- Portenoy et al. Long-term use of controlled-release oxycodone for noncancer pain: results of a 3-year registry study. Clin J Pain. 2007;23:287-299.
- Zech et al. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. Pain. 1995;63:65-76.

Self-Assessment Test

Circle the best response

1). Which of the following is not a KADIAN® capsule strength?
  a. 20mg
  b. 50mg
  c. 80mg
  d. 150mg

2). Which of the following is true regarding KADIAN® administration?
  a. Administer orally every 12 or 24 hours.
  b. Administer with meals.
  c. Mix with applesauce and place in a 16-French or larger G-tube.
  d. Sprinkle contents into applesauce up to 48 hours before ingestion.

3). Which of the following is true regarding the bioequivalence of KADIAN®?
  a. KADIAN® is bioequivalent to other long-acting morphine products.
  b. The area under the curve (AUC) of KADIAN® is similar to that of other controlled-release morphine products.
  c. The C_{max} achieved with KADIAN® is greater than the C_{max} achieved by other controlled-release morphine products.
  d. The slow release of morphine sulfate from KADIAN® reduces the area under the curve (AUC).

4). In patients who have not previously received opioids, the initial KADIAN® dose is:
  a. 20 mg every 24 hours
  b. 30 mg every 24 hours
  c. 20 mg twice daily
  d. 30 mg twice daily

5). When converting from parenteral morphine to oral morphine, the literature suggests giving an oral dose ______________times greater than the parenterally administered dose.
a. 3 to 6
b. 5 to 10
c. 10 to 20
d. at least 100

True or False

6). When converting patients from other oral morphine preparations to KADIAN®, the initial once-daily KADIAN® dose would be equivalent to the patient's current total daily morphine dose every 24 hours.
a. True
b. False

7). Excessive opioid side effects soon after conversion to KADIAN® should be treated by discontinuing KADIAN®.
a. True
b. False

8). Any breakthrough or incident pain may be treated with a short-acting opioid analgesic.
a. True
b. False

9). A patient's KADIAN® dose can be increased every 24 hours.
a. True
b. False

10). KADIAN® impairs the central nervous system and motor skills less than do other opioids.
a. True
b. False

Answers to Self-Assessment Test

1. d	6. a
2. a	7. b
3. b	8. a
4. a	9. b
5. a	10. b

CHAPTER TEN

Safety and Adverse Experiences

Learning Objectives

After reading this chapter and completing the self-assessment test, you should be able to:

- Discuss the common adverse effects of KADIAN® and other opioids.
- Describe the potential serious adverse effects of KADIAN® and other opioids.
- Discuss the abstinence syndrome that can occur when chronic opioids are discontinued.
- Discuss the clinical manifestations of opioid overdose.
- Understand the use of opioids in pregnancy, labor and delivery, and breastfeeding.
- Identify the contraindications and precautions to the use of KADIAN®.
- Discuss potential drug interactions involving KADIAN®.

Terminology

Addison's disease:	A deficiency of the adrenal cortex and therefore the hormones produced in this area.
Amblyopia:	Weakness in vision in one eye that can cause it to relax and drift relative to the other (also called *lazy eye*).
Amenorrhea:	Lack of menstrual periods.
Ames test:	A test for potential carcinogenic properties of a drug. It uses the rate of genetic mutations caused in a strain of the bacterium *Salmonella*.
Amylase:	An enzyme that occurs in saliva and pancreatic juice and aids the digestion of starch. Amylase will also hydrolyze glycogen to yield glucose and other sugars.
Anaphylaxis:	A severe, life-threatening allergic reaction.
Antiemetic:	A drug that prevents nausea.
Arthralgia:	Joint aching.
Ataxia:	A lack of coordinated muscular movements that can result from neurologic disorders.
Atelectasis:	Collapse of the alveoli (tiny air sacs) in the lungs.
Axial skeletal fusion:	Calcification of the spinal column that leads to calcified connections between the bones, leading to a loss of motion.
Black box warnings:	Warnings required by the FDA for a product. They are called "Black Box" because they are required to be placed in a black box in a prominent position in the pharmaceutical information for a given drug ("package insert").
Biliary colic:	Abdominal pain that results from obstruction of the biliary tree (bile ducts or gallbladder).
Bradycardia:	Low heart rate.
Carcinogenic:	Any substances producing cancer.
Cimetidine:	A drug that reduces the production of stomach acid (also called Tagamet®).
Cordotomy:	A surgical procedure involving the division of the spinothalmic tract. The spinothalmic tract contains the nerve fibers responsible for transmitting the sensation of pain up the spinal cord.
Cytochrome (CYP) P450 isoenzymes: Liver enzymes that metabolize drugs.	
Decubitus ulcer:	An ulceration of the skin caused by pressure over a bony prominence.
Delirium tremens:	An alcohol withdrawal syndrome that results in confusion and hallucinations (DTs).
Detrusor muscle:	The muscle in the bladder that contracts to initiate urination.

Diaphoresis:	Sweating.
Edema:	Excessive accumulation of fluid in a tissue.
Embryocidal:	Causes death of an embryo in pregnant women.
Encephalopathy:	A disease or process causing abnormalities in the tissue of the brain.
Flaccidity:	A decrease in muscle tone.
Gastric stasis:	A relaxation of the stomach that causes it to not digest or propel its contents into the small intestine.
Hypercapnia:	The presence in the blood of an unusually high concentration of carbon dioxide.
Hyperpyrexia:	Increased body temperature (fever).
Hyperreflexia:	Excessively increased reflexes.
Hypotension:	Low blood pressure.
Hypothyroidism:	Low levels of thyroid hormones.
Hypoxia:	A deficiency of oxygen in a tissue.
***In vitro*:**	Within a test tube.
***In vivo*:**	Within the living body.
Inappropriate ADH secretion:	A syndrome in which antidiuretic hormone (ADH) is secreted abnormally.
Intraperitoneal:	Within the membrane of the abdominal cavity.
Kyphoscoliosis:	Abnormal curvature of the spine both forward and sideways.
Lethargy:	Extreme drowsiness from which it is difficult to rouse an individual.
Leukocytes:	White blood cells.
Malaise:	A generalized uncomfortable feeling that may be accompanied by physical discomfort.
Metastases:	The distant spread of a malignant tumor from its site of origin.
Miosis:	Contraction of the pupils.
Monoamine oxidase inhibitor:	A type of drug used to treat depression.
Mouse micronucleus test:	This is a commonly used test that determines whether a compound is able to cause chromosome aberrations in mice. It is used to predict genotoxicity (teratogenicity) of a new drug.
Mutagenic:	An agent that increases the rate of mutation.
Myalgia:	Pain in the muscles.
Myoclonic jerks:	Mild to moderate muscle contractions.
Myxedema:	A dry, firm, waxy swelling of the skin and subcutaneous tissues found in patients with underactive thyroid glands.
Noncardiogenic pulmonary edema:	A build-up of fluid in the lungs that is not caused by heart failure.

Nystagmus:	An abnormal sideways or up-and-down movement of the eyes that is associated with neurologic abnormalities or disease of the vestibular apparatus of the ear.
Pallor:	Paleness.
Pancuronium:	A drug used in anesthesia that paralyzes skeletal muscle.
Paralytic ileus:	Loss of motility of the small intestine.
Prostatic hypertrophy:	Enlargement of the prostate gland.
Q24h/Q12h:	Shorthand for every 24 hours and every 12 hours. Q is an abbreviations for *every* from the Latin *quaque*.
Rhinitis:	Inflammation of the mucous membranes of the nose.
Stomach atony disorder:	A condition caused by a loss of muscle tone in the stomach. It can lead to pain, nausea and vomiting, and distension.
Syncope:	Fainting.
T-cells:	White blood cells primarily responsible for cell-mediated immunity.
Teratogen:	An agent that induces the formation of abnormalities of the fetus.
Toxic psychosis:	Alterations of mental state caused by drug toxicity.
Urethral stricture:	Narrowing of the passage through which urine is voided.
Vasopressors:	Drugs that stimulate the contraction of blood vessels and therefore bring about an increase in blood pressure.
Vertigo:	Dizziness, specifically the type that causes a spinning sensation.

Introduction

The benefit of opioid therapy is generally very favorable when treatment is optimized. However, these medications do have potentially significant adverse effects. In addition, there are specific patient populations who should avoid or exercise caution when using KADIAN® and other opioids. Patients taking medications that cause sedation or central nervous system depression, phenothiazines, general anesthetics, or vasodilatory or other drugs that lower blood pressure should also be aware of the potential for serious adverse events when such medications are used concomitantly with opioids. This chapter will review the clinical presentations of these safety issues.

Opioid Adverse Reactions

The adverse effects of morphine, and therefore KADIAN®, are essentially the same as those observed with other opioid analgesics. Serious adverse reactions that may be associated with KADIAN® include:

- respiratory depression,
- respiratory arrest,
- circulatory depression,
- cardiac arrest,
- hypotension, and
- shock.

The less severe adverse effects include

- drowsiness,
- dizziness,
- constipation, and
- nausea and vomiting.

Adverse reactions are more likely to occur in opioid-naïve patients or with dosage increases in opioid-tolerant patients. In addition, the risk of an adverse effect increases as the dose of the opioid increases. Fortunately, most adverse effects are temporary. They will cease or decrease as opioid therapy is continued and some

degree of tolerance develops. Adverse effects should be expected and managed as a part of opioid analgesia.

Management of Constipation

Virtually all patients suffer from constipation while taking opioids chronically. Tolerance does not usually develop to this side effect. Thus, it requires an aggressive preventive approach, regular assessment, and aggressive management if symptoms are detected. Exercise, adequate fluid intake, eating bulk-containing foods, and taking natural colon stimulants such as prune juice will help to prevent constipation. The most common approach is to use a laxative regularly. Treatment continues as long as the patient takes opioids.

Management of Nausea and Vomiting

Nausea and vomiting are common after single doses of opioids or as an early undesirable effect of chronic opioid therapy. Vomiting accompanies nausea more often when constipation is not well controlled. Prophylactic treatment of nausea is not recommended because tolerance usually develops after several days. However, it may be necessary to use a scheduled antiemetic for the first week of therapy. A reduction in the dose by 10%-25% may also help reduce nausea. Persistent nausea and vomiting may be due to gastric stasis. Gastric stasis can be treated with metoclopramide, a drug that increases gut motility.

Management of Sedation

Most patients experience drowsiness at the onset of therapy or with a dose change. Tolerance to sedation usually develops over several days. If significantly sedated, patients should be discouraged from driving and operating mechanical equipment. Excessive or persistent sedation should be investigated. Factors that contribute to persistent sedation include the following: intolerance to the dose used, concurrent sedative medications, the presence of hepatic or renal insufficiency, hypoxia or hypercapnia due to exacerbated respiratory failure, disease severity, and the patient's general condition. If sedation continues, it can be managed with central nervous system stimulants such as methylphenidate, dexamphetamine, or modafinil.

Management of Myoclonus

Patients taking high doses of opioids often experience myoclonic jerks. If it disrupts sleep or causes an exacerbation of pain (e.g., bone metastases) changing to

another opioid may help. Mild myoclonus is common and resolves as tolerance develops. It can be treated with low doses of diazepam or clonazepam and other benzodiazepines.

Management of Skin Reactions

The itching, flushing, and rash that can occur because of the release of histamine will typically resolve in less than 2 weeks. Patient symptoms can be treated with antihistamines.

KADIAN® Clinical Safety

Clinical trials are often the best means of determining adverse event rates. KADIAN® has been evaluated in several clinical trials that have shown that its adverse events are similar to those of other opioids. These data were collected from several clinical studies of volunteers or patients who received KADIAN® in single doses or in repeated doses for periods of up 7 to 14 days. Brief descriptions of the adverse event data from each of the repeated-dose studies (i.e., studies simulating typical clinical conditions) are presented below:

Broomhead A, et al. *J Pain Symptom Manage* 1997;14(2):63-73.

This parallel-group clinical study evaluated adverse event data collected over a 7-day treatment period for 61 patients receiving KADIAN® q24h, 52 patients receiving KADIAN® q12h, and 56 patients receiving MS Contin® q12h for treatment of moderate to severe cancer-related pain.

Central nervous system adverse events judged to be related to treatment had the highest frequency of adverse events: 11.5% in the KADIAN® q24h group, 13.5% in the KADIAN® q12h group, and 1.8% in the MS Contin® group. Despite the administration of high doses of morphine once daily in the morning in the KADIAN® q24h group, there was no significant difference among treatment groups for "nervous system" or other categories of adverse events. The incidence of emergent adverse events was acceptable for all three treatment groups given the patient population and the known side effects of morphine.

Floter T, et al. *Clin Drug Invest* 1997;14(3):183-191.

This parallel-group clinical study evaluated adverse event data collected over a 14-day treatment period for 104 patients receiving KADIAN® q12h and 74 patients receiving MS Contin® q12h for treatment of moderate to severe malignant or nonmalignant pain. Typical morphine-related adverse events were reported with a comparable incidence in both treatment groups: 24% for patients receiving KADIAN® q12h and 26% for patients receiving MS Contin® q12h.

Gourlay GK, et al. *Pain* 1997;69:295-302.

This two-period crossover study evaluated adverse events during 7-day treatment periods for 24 patients receiving KADIAN® q24h and MS Contin® q12h for treatment of severe cancer pain.

Both KADIAN® and MS Contin® q12h were associated with a low incidence of side effects. There were no significant differences between treatment groups in the incidence of nausea and vomiting, constipation, sedation, or appetite suppression. The only significant difference was observed on day 5 of treatment, when the incidence of confusion was higher in the KADIAN® q24h group. This difference, however, was considered a chance event because the assessments for confusion on the other assessment days were not significantly different.

Kerr RO, Tester WJ. *Clin Drug Invest 2000;19(1):25-32.*

None of the comparisons of tolerability between KADIAN® q24h and MS Contin® q12h had statistically significant differences. Most adverse events were those expected to occur with morphine, and the frequency and severity of morphine-related adverse events (nausea and vomiting, constipation, sedation, confusion, and appetite) for the KADIAN® treatment period were comparable with those for the MS Contin® treatment period. The percentage of patients who dropped out of the study because of adverse events (8% for KADIAN® and 5% for MS Contin®) and the percentage of patients experiencing serious adverse events (8% for KADIAN® and 9% for MS Contin®) were comparable during the KADIAN® and MS Contin® treatment periods.

Adverse Events - Single Dose and Repeated Dose

In controlled clinical trials in patients with cancer pain, the most frequently reported adverse events thought to be related to KADIAN® were drowsiness (9%), constipation (9%), nausea (7%), dizziness (6%), and anxiety (6%). Other less common side effects expected from morphine or seen in less than 3% of patients in the clinical trials are listed below.

- **Body as a Whole:** asthenia (muscular weakness), accidental injury, fever, pain, chest pain, headache, diaphoresis, chills, flu-like syndrome, back pain, malaise, withdrawal syndrome
- **Cardiovascular:** tachycardia, atrial fibrillation, hypotension, hypertension, pallor, facial flushing, palpitations, bradycardia, syncope
- **Central Nervous System:** confusion, dry mouth, anxiety, abnormal thinking, abnormal dreams, lethargy, depression, tremor, loss of concentration, insomnia, amnesia, paresthesia (abnormal sensation), agitation, vertigo, foot drop, ataxia (altered gait), hypesthesia (decreased sensation of touch), slurred speech, hallucinations, vasodilation, euphoria, apathy, seizure, myoclonus
- **Gastrointestinal:** vomiting, anorexia, dysphagia (difficulty swallowing), dyspepsia (heartburn), diarrhea, abdominal pain, stomach atony disorder, gastroesophageal reflux, delayed gastric emptying, biliary colic
- **Endocrine:** hyponatremia (low blood sodium) due to inappropriate ADH secretion, gynecomastia (breast development in males)
- **Hemic & Lymphatic:** anemia, leukopenia (low white blood count), thrombocytopenia (low platelet count)
- **Metabolic & Nutritional:** peripheral edema, hyponatremia (low sodium levels), edema
- **Musculoskeletal:** back pain, bone pain, arthralgia
- **Respiratory:** hiccup, rhinitis (runny nose), atelectasis, asthma, hypoxia, dyspnea (shortness of breath), respiratory insufficiency, voice alteration, depressed cough reflex, noncardiogenic pulmonary edema.
- **Skin and Appendages:** rash, decubitus ulcer, pruritus (itching), skin flush
- **Special Senses:** amblyopia, conjunctivitis, miosis, blurred vision, nystagmus, diplopia (double vision)
- **Urogenital:** urinary abnormality, amenorrhea, urinary retention, urinary hesitancy, reduced libido, reduced potency, prolonged labor